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Nano-Based Drug Delivery in Cancer: Tumor Tissue Characteristics and Targeting

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Abstract

Cell mutations are the root cause of cancer. Mutated cells outgrow healthy ones, starving them of oxygen and nutrients as they proliferate. This condition is managed using a variety of approaches, including surgery, chemotherapy, radiation treatment, or a mix of these. Common treatment approaches are costly and do huge damage due to their energy-intensive and labor-intensive treatment cycles and their destruction of both healthy and sick cells. Cancer is one of the most difficult illnesses to treat. Much progress in the management of this illness has coincided with the growth of our understanding of it. Still, one of the therapeutic issues is the toxic effects of chemotherapy medications, which are typically seen as a result of their non-specific action. Inventions in drug delivery methods within the last 20 years have helped alleviate some of the chemotherapy-related issues. Nanoparticles comprising both organic and inorganic substances are part of these systems. While many of these systems are still in the pre-clinical phase, a few have broken into the pharmaceutical industry. Modern nanoparticles have solved the problem of drug-resistant cells and opened up a new area of cancer therapy; this articleexplores medication delivery to tumor tissue, a method that is more successful than traditional methods of drug delivery.

Keyword: Cancer, Drug, Targeted transfer, Nanoparticles, Chemotherapy, Ligand, Liposome maisel

Introduction

Cancer is a leading cause of death worldwide and needs to be rapidly identified and treated with effective antitumor therapies. Nanotechnology plays a key role in this as it delivers drugs specifically to cancer cells, thereby minimizing unwanted side effects. This offers clear advantages for cancer therapeutics [1-3]. Theragnostic is a radiopharmaceutical-based approach to personalized medicine and nuclear medicine, which uses 1 radiopharmaceutical to detect tumors and a second to treat them. One of the earliest applications of theragnostic was the use of iodine isotope 131 to diagnose and treat thyroid cancer in the field of nuclear medicine. In nuclear medicine, different chemicals are used individually or in combination for diagnostic imaging and targeted therapy [4-7]. Some of these chemicals (e.g. iodine) enter the target via metabolic processes, whereas others, such as receptor ligands, are already present in the target tissue. Theragnostic uses these processes to enable image-based localization of diseased tissues and radiation-based targeted ablation of these tissues [8-11]. Therapeutics is a synergistic field that combines diagnosis and therapy. Nano sensors and nanomedicine arose from the realization that the use of nanoscale particles offers many advantages in diagnosis and therapy. The term “nanotherapeutics” refers to the practice of utilizing and improving nanomedicine strategies for advanced therapeutic purposes. Nanocarriers such as polymer conjugates, gold-based nanomaterials, silicon dioxide-based nanomaterials, dendrimers, micelles, liposomes, metallic and inorganic nanoparticles, carbon nanotubes, and nanoparticles made from biodegradable polymers have been used and improved [12-15]. These carriers are used for precise and specific delivery of diagnostic and therapeutic agents with the goal of improving therapeutic efficacy while minimizing potential side effects. Incorporation of targeting moieties into advanced therapeutic nanomedicines allows them to identify and bind specific targets and allows for internalization via mechanisms such as receptor-mediated endocytosis. Gold nanoparticles have been widely studied for their potential as versatile sensors [16-19]. Gold nanomaterials can be tailored for specific applications by manipulating their shape. For example, gold nanoparticles, nanorods, nano shells, and nanocages each have different thermal and optical properties that can be used for therapeutic purposes [20-22]. Nanotheragnostics, which are PEG nanocarriers, have a long residence time in the body, are stable, and gradually become immunogenic and antigenic. PEG-containing nano theragnostic liposomes are often used for cancer detection and treatment.

Cancer therapeutics refers to the combination of cancer diagnostic and therapeutic technologies to reduce the burden on patients and shorten the treatment period. Cancer therapeutics form the basis of personalized cancer treatment [23-25]. Applying technologies that slow the progression of cancer at the diagnostic stage could dramatically improve treatment outcomes. In this way, we hope to reduce the overall severity of the disease by slowing its spread or slowing its progression [26-29]. This is in line with the goal of a tailored cancer treatment, clearly outlined in the principles of cancer therapeutics. Nanomedicine, i.e. treatments based on nanoparticles composed of various organic and inorganic nanomaterials, plays a key role in the treatment, diagnosis, monitoring and control of biological systems [30-33]. The anticancer therapeutic properties of these nanostructures include their ability to encapsulate drugs, target cancer cells or surface-bound molecules, and monitor treatment responses to modulate drug efficacy and safety. There are 2 main methods for targeting nanostructures to cancer cells (**Figure 1**): Passive targeting of abnormal tumor cells, where nanostructures penetrate and accumulate due to disturbances in tumor cell physiology and structure, and active molecular targeting, which is based on recognition mechanisms such as ligand-receptor and antigen-antibody. For the successful development and production of targeted therapeutic nanoparticles for cancer treatment, several criteria must be met. Most importantly, appropriate biomarkers must be identified that are abundant in cancer cells but rare in healthy cells [34,35]. The appropriate targeting ligand should bind to the receptor with high specificity. Besides, the application must be mass-produced. The development of therapeutic drugs requires

nanoparticles that are stable, biocompatible, biodegradable and have low toxicity. These nanoparticles should also be able to release therapeutic substances after penetrating into the tumor tissue or cancer cells [36-39]. One of the many approaches to cancer treatment is photothermal therapy, which uses gold or carbon nanotube nanoparticles to generate heat and kill tumor cells in the area. Photodynamic therapy is another approach that uses nanoparticles in combination with photosensitizers to generate reactive oxygen species that kill tumor cells and improve the effectiveness of radiation, chemotherapy, and gene therapy [40-42]. Theragnosis is a new medical term that describes the integration of treatment and diagnosis. Theragnosis bridges the gap between diagnosis and treatment, allowing cancer patients to receive more accurate diagnosis and personalized treatment [43-45]. The benefits of therapeutics include improving the efficacy of anticancer drugs by monitoring the accuracy of anticancer drugs on patients' tumors during and after treatment, providing immediate access to personalized targeted therapy, and simultaneously diagnosing and treating patients with early cancer. This offers promising prospects for reducing cancer-related mortality, especially for individuals at later stages of the disease [46-49].

Chen *et al.* [17], several high-tech imaging modalities, such as X-rays, ultrasound scans, computed tomography scans, radionucleotide imaging, and magnetic resonance imaging, play an important role in the diagnosis and treatment of cancer in clinical settings. However, these imaging techniques cannot identify the location of cancer cells or surface markers for targeted cancer therapy. New therapeutic approaches using highly sensitive probes are needed to accurately diagnose and specifically treat cancer [50-53]. Nanomedicine represents a revolutionary force in modern medicine, but although the creation and use of nanoparticles has been around for centuries throughout history, nanomedicine as an interdisciplinary field was only formally introduced in the 1990s. Scientists in physics, chemistry, and biology paved the way for this new field by using sub-microscopic tools to delve into the study of cellular, molecular, and atomized structures [54-57]. The nanotechnology approach first proposed by Feynman in the 1950s marked a key point in rise of nanomedicine to prominence in scientific research and medical practice. The initial rapid growth of nanomedicine was driven by remarkable methodological advances, and its historical development and diversification into many medical applications, such as tissue engineering, are well documented [58-60]. Notable research and application areas include the use of biosensors in lab-on-a-chip and nanoimaging diagnostic applications, as well as the use of biocompatible nanomaterials (e.g., liposomes) as therapeutic vehicles for genes, vaccines, and drugs. These Nano capsules are particularly promising in cancer treatment in combination with hyperthermia, thermal ablation, and radiation therapy [21].

Cancer treatment nowadays often involves invasive procedures such radiation therapy, surgery to remove tumors if feasible, primary chemotherapy to decrease existing malignant masses, and catheter-based chemotherapy [1-4]. Cancer cells divide and expand at a higher rate than healthy cells, making them more susceptible to the harmful effects of radiation and chemotherapy [61-64]. Current chemotherapy research aims to design drug carriers with alternative drug entry routes, identify novel therapeutic targets such tumor-feeding blood veins, and create more precise and targeted drug formulations. The capacity of a therapy to eradicate cancer cells while sparing healthy cells is a key component of its efficacy [65-68]. At this time, the inability of cancer chemotherapeutic medications to specifically target cancer cells is a major limitation. Besides, harmful side effects are caused by the limited therapeutic index of most anticancer medicines. When certain cancer cells develop resistance to chemotherapy, the only options for treatment are to either raise the dosage of the medicine or utilize several treatments simultaneously [69-73]. However, the drug's toxicity increases with these measures as well. There are a number of drug delivery methods that have been created with the aim of improving current medications and reducing their adverse effects. These systems include microparticles, soluble drug-polymer conjugates, polymer micelles, nanoparticles, and liposomes. In the meanwhile, nanoparticles - which can be made using biocompatible polymers and have a simpler manufacturing method - have been getting a lot of interest

[74-78]. This phenomenon of enhanced permeability and retention (EPR) [19] occurs because tumor-associated blood vessels are more permeable than normal-tissue-associated blood vessels, and because tumor-associated blood vessels need more oxygen and nutrients to fuel their rapid growth.

Clinical and preclinical settings use drug delivery systems (DDS) to provide therapeutic chemicals for the treatment of disorders [79-82]. Traditionally, DDS have been administered intravenously or orally. Traditional DDS offer numerous benefits, such being easy to administer and having high patient acceptability, but they also have several limits and downsides, such as [83-85]:

1) Poor biodistribution makes oral administration an unsuitable choice for medications that need organ-specific targeting; also, there is a lack of selectivity.

2) Toxic effects on detoxifying organs like the liver and kidneys might result from excessive drug absorption into these tissues.

3) Many of the problems with conventional medication administration methods may be solved using controlled drug delivery systems.

For instance, conventional cancer treatments like chemotherapy have a history of nonspecific drug distribution that damages healthy cells as well as cancer cells, leading to poor effectiveness and significant toxicity [86-88]. By targeting the tumor, controlled DDSs may increase drug concentrations in cancer cells while minimizing damage to normal cells, making them ideal carriers for chemotherapeutic medicines [89-91]. Because controlled DDSs can keep drugs safe from clearance and degradation, they are great for protein delivery and innovative treatments like gene therapy and RNA interference, which can keep DNA and siRNA out of the reticuloendothelial system and other tissues' uptake as well as enzymatic degradation [92].

Nanoparticles are now being considered as potential options for controlled medication delivery systems, thanks to advancements in nanotechnology. Particles having dimensions ranging from 10 to 1,000 nm are called nanoparticles. In the context of drug delivery systems (DDS), they have the potential to boost the effectiveness of medications via regulated or sustained release, prolong the half-life of pharmaceuticals, and even make certain hydrophobic compounds more soluble. To further aid in toxicity reduction and medication biodistribution management, stimuli-responsive nanoparticles have been developed. The first DDS nanoparticles, known as liposomes, were developed in the 1960s and utilized to transport drugs and proteins [6]. The number of materials being transformed into nanoparticles and used as DDS has increased significantly since then (**Figure 2**). There are 77 items undergoing clinical trials, and 51 nanoparticles have been authorized by the FDA, according to Alimoradi *et al.* [7]. The bulk of nanoparticle-approved products are either polymeric or liposomal. On the other hand, scientists think that nanoparticle DDS can also be made from more complicated materials including micelles, metals, and materials based on proteins. Three distinct nanoparticle DDS kinds, representing 3 distinct nanoparticle manufacturing material sources, are the subject of this report: Silica nanoparticles manufactured from inorganic materials; Polylactic-co-glycolic acid (PLGA) nanoparticles made from synthetic polymeric materials. The presentation covers their techniques of manufacture as well as their uses in medication delivery for cancer treatment.

Current and potential challenges to clinical usage of nanoparticles, as well as future advancements in nanoparticle DDS, are also covered. Cancer treatment nowadays often involves invasive procedures such radiation therapy, surgery to remove tumors if feasible, primary chemotherapy to decrease existing malignant masses, and catheter-based chemotherapy [93-95]. Radioactive and chemotherapeutic treatments are most effective against cancer cells because these malignant cells divide and proliferate at a much quicker rate than normal cells in the body [96-98]. Drug carriers with alternative drug entry routes, novel treatment targets (such as blood vessels feeding tumor tissue), and the development of targeted and particular drug forms are all areas where chemotherapy research is now focused. The capacity of a therapy to eradicate cancer cells while sparing healthy cells is a key component of its efficacy [99-101]. Cancer treatment is now hindered by the fact that medications do not selectively target cancer cells. The harmful side effects

of most anticancer medicines are a result of their weak therapeutic index. When certain cancer cells develop resistance to chemotherapy, the only options for treatment are to either raise the dosage of the medicine or utilize several treatments simultaneously [12-15]. Although these techniques are effective, they also increase the drug's toxicity. Several drug delivery technologies, such as soluble drug-polymer conjugates, polymer micelles, nanoparticles, liposomes, and microparticles, have been created with the aim of reducing these adverse effects and improving current medications. However, nanoparticles, which may be made using biocompatible polymers and have a simpler manufacturing procedure, have recently attracted considerable interest [16-18]. There is a phenomenon known as enhanced permeability and retention (EPR) [19]. This is because the blood vessels surrounding tumor tissue are more permeable than those surrounding normal tissues. Besides, the tumor tissue is growing at a faster rate, so it needs more oxygen and nutrients. Consequently, there is a better chance that the drug will be absorbed.

Clinical and preclinical settings use drug delivery systems (DDS) to provide therapeutic chemicals for the treatment of disorders [1]. Traditionally, DDS have been administered intravenously or orally. Traditional drug delivery systems (DDS) have many benefits, like good patient acceptance and ease of administration, but they also have many limitations and drawbacks [102-105]:

1) Poor biodistribution from oral administration, which makes them less than ideal for drugs that need to be targeted to specific organs; lack of selectivity.

2) The liver and kidneys, which filter out harmful substances from the blood, may become poisonous if medications are absorbed into them in large quantities.

When compared to more conventional methods, controlled medication delivery systems have various advantages. For instance, conventional cancer treatments like chemotherapy have a history of nonspecific drug distribution that damages healthy cells as well as cancer cells, leading to poor effectiveness and significant toxicity [2]. Because they can target the tumor and increase medication concentrations in cancer cells while limiting toxicity in normal cells, controlled DDSs are great chemotherapeutic drug carriers [3,4]. As an added bonus, controlled DDSs can prevent drugs from being broken down or cleared out, which make them great for protein delivery and other novel therapeutic methods like gene therapy and RNA interference. These methods can aid in avoiding reticuloendothelial or other tissues' uptake of DNA or siRNA, as well as enzymatic degradation [5].

Thanks to recent developments in nanotechnology, nanoparticles have emerged as strong contenders for regulated medication delivery systems. Anything with a diameter between 10 and 1,000 nm is considered a nanoparticle. When used as DDS, they have the ability to prolong the half-life of pharmaceuticals, make some hydrophobic compounds more soluble, and enhance the efficiency of medications via controlled or sustained drug release. Another useful use for stimuli-responsive nanoparticles is to regulate medication biodistribution and lessen toxicity. In the 1960s, liposomes were used as carriers for drugs and proteins; they were the first nanoparticle DDS to be found [6]. A growing number of materials have been subjected to nanoparticle processing and used as DDS since then (**Figure 2**).

There are 77 items undergoing clinical trials, and 51 nanoparticles have been authorized by the FDA, according to Alimoradi *et al.* [7] in 2016. The vast majority of nanoparticle materials are either polymeric or liposomal. Nanoparticle DDS may also be made from simpler materials, but scientists think that micelles, metals, and materials derived from proteins are the most promising.

Three distinct nanoparticle DDS kinds, representing 3 distinct nanoparticle manufacturing material sources, are the subject of this report: Aqueous silica nanoparticles and synthetic polymeric polylactic acid (PLGA) nanoparticles are some examples of nanomaterials. We will go over how they are made and how they may be used in cancer treatment medication delivery. Also covered are potential future advances of nanoparticle DDS as well as current challenges that nanoparticles may encounter in clinical application. Modern nanoparticles have solved the problem of drug-resistant cells and opened up a new area of cancer therapy; this article explores medication delivery to tumor tissue, a method that is more successful than traditional methods of drug delivery.

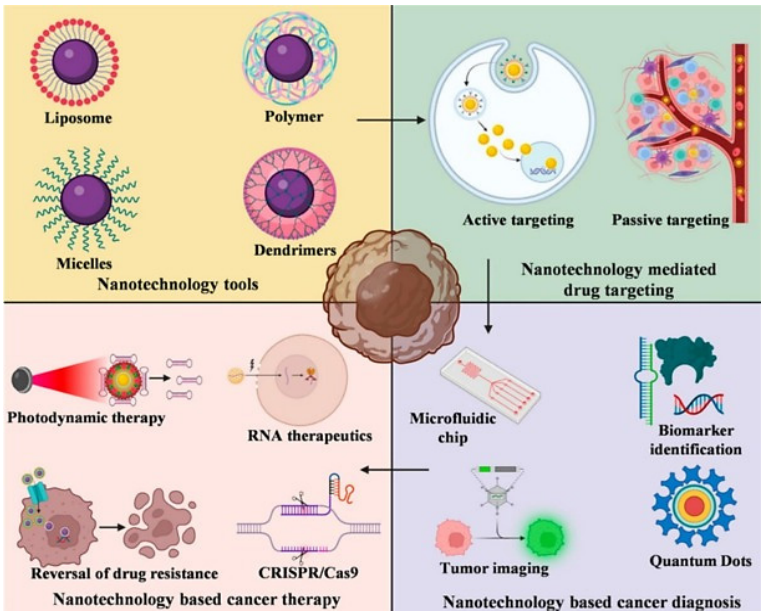

Figure 1 Nano tools-based cancer targeting diagnosis and treatment [24].

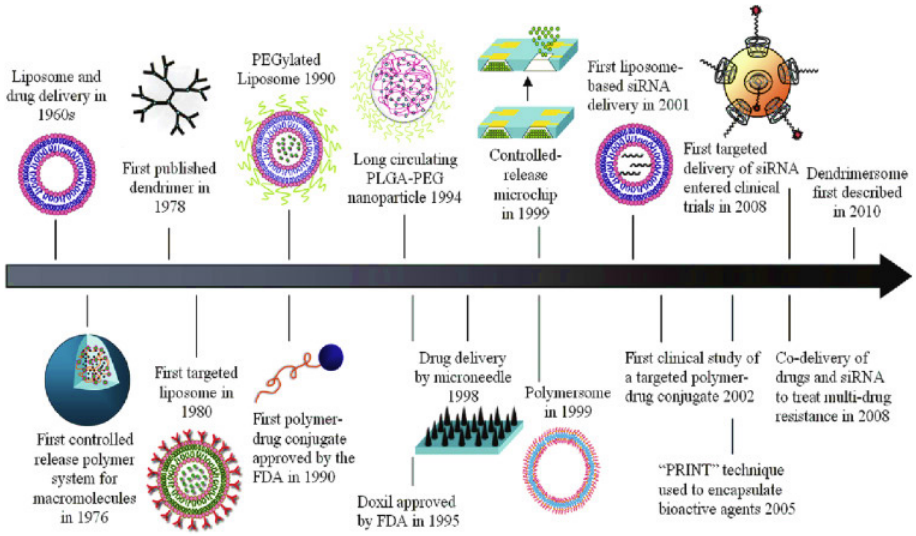

Figure 2 Project timeline for the creation of medication delivery systems using nanoparticles [25].

Targeted drug delivery

Both active and passive prototyping are part of targeted medication administration. Passive targeting involves the medication and carrier passively reaching the target cells and tissues, whereas active targeting involves the binding of the therapeutic drug or carrier to particular tissues or cells [20-22]. The biological restrictions that conventional medications have may be circumvented by carefully engineered nanoparticles. Even though they are unable to cross through, they do so with ease. The hyperosmotic activity of mannitol opens the tight junctions, allowing nanoparticles to pass the blood-brain barrier, according to studies. Thus, this approach may be used for the administration of drugs in a sustained release form to address complex conditions like brain tumors [23-26].

Passive targeting

Nano frameworks can latently target tumor tissue by misusing its auxiliary highlights. When tumors reach a

volume of 2 mm^3 or more, their penetrability gets to be constrained. This restriction disables their capacity to retain nourishment and squander items and to supply oxygen to cells. To overcome this issue, tumor tissue starts the method of angiogenesis [27,28]. This wonder is characterized by variations from the norm within the storm cellar film, the nonappearance of an endothelium covering peristalsis, and the coming about arrangement of cracked blood vessels with pores and fenestrations extending in measure from 100 to 1,200 nm. The measure of the pores changes depending on the sort of tumor. Besides, due to the absence of an effective lymphatic framework, tumor tissue features a higher interstitial weight at the center of the tumor than within the encompassing zones. This expanded inner weight leads to surge of interstitial liquid, decreasing the discharge of drugs into the tumor center. It has been found that tumor tissue can capture plasma proteins and utilize their corruption items for multiplication [29].

Passive targeting using leaky tumor capillary networks

Passive Targeting Using Leaky Tumor Capillary Networks Many nanodrug delivery systems exploit the enhanced permeation and retention (EPR) properties of tumor tissue (**Figure 3**) [29]. This property is due to 2 properties of tumor tissue: a) the capillary endothelium of malignant tissue is irregular and more permeable to macromolecules than healthy tissue, allowing the release of drug nanocarriers from the vessels blood of tumor endothelium; and b) lack of lymphatic drainage from the tumor bed causing the drug to remain in the area [30,61-64]. By combining chemotherapeutic drugs with appropriate polymers or carriers, drug accumulation in the target tissue can be increased 10 to 100-fold compared to free drug [31,65-67].

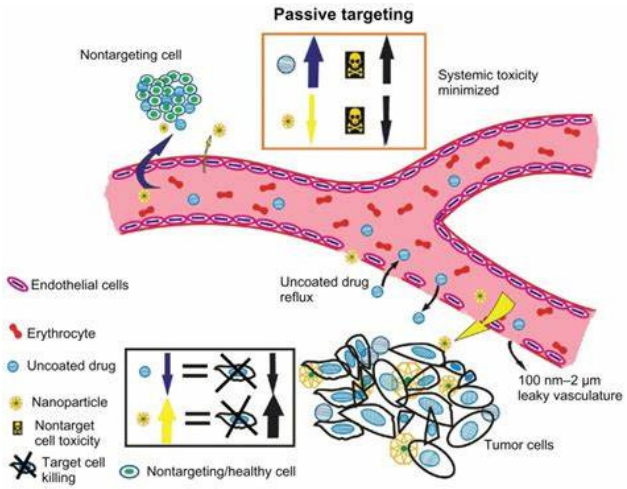

Figure 3 Passive targeting using tumor leaky capillary network [29].

Passive targeting using tumor tissue environment

Enzyme targeting

Another type of passive targeting relies on the characteristics of the tumor tissue environment. The drug is injected into the patient in an inactive form and then converted to an active form under certain conditions [68,69]. For example, the inactive and nontoxic anticancer drug "choline phospholipid lipid ether" is converted to the active and toxic phospholipid lipid choline ether by phospholipase A2, which is abundant in the tumor environment. Now, when anticancer drug-loaded liposomes are created using inactive phospholipids, these liposomes simultaneously enter the tumor environment and come into contact with phospholipase A2 [70,71]. In addition to destroying and releasing drugs, the structural units of liposomes are also converted into an active form. In doing so, it kills tumor cells in 2 ways (**Figure 4**) [32].

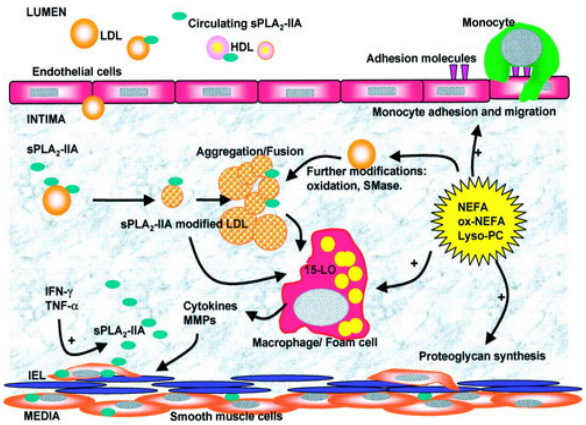

Figure 4 Phospholipase A2 (sPLA2), present in high amounts at tumor sites, is capable of converting the inactive chemical structure of the prodrug into the active form. When the liposomes enter the tumor site, this enzyme breaks them down and releases the drug [32].

Targeting based on environmental acidity

The over-the-top development and multiplication of cancer cells powers them to utilize other strategies, such as glycolysis, in expansion to normal strategies of getting vitality, but these strategies cannot meet the requirements digestion system and get oxygen and vitality. This makes a somewhat acidic environment around the tumor. Researchers have taken advantage of this characteristic of tumors by planning and fabricating drug-containing polymer nanoparticles whose composition changes in an acidic environment. There are 2 issues with this approach [33]; a) the acidic environment is expelled from the tumor, so the medicate is discharged some time recently it can reach the tumor, in this manner causing harm to the tissues encompassing the tumor; and b) since the tumor sharpness isn't much lower than the body's natural environment (around 6.5), creating drug-free nanoparticles within the body's normal environment is exceptionally challenges and challenges tumor environment (**Figure 5**) [33,34].

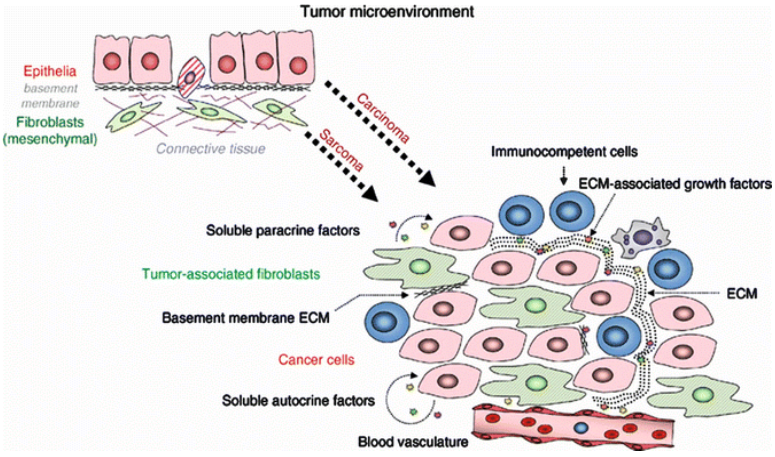

Figure 5 Schematic Targeting based on environmental acidity [33].

Targeting based on temperature changes

Due to their tall action, the temperature of the tumor environment is marginally higher than the typical body environment, and this property can be ideally utilized by advancement of temperature-sensitive therapeutic nanoparticles (**Figure 6**) [33].

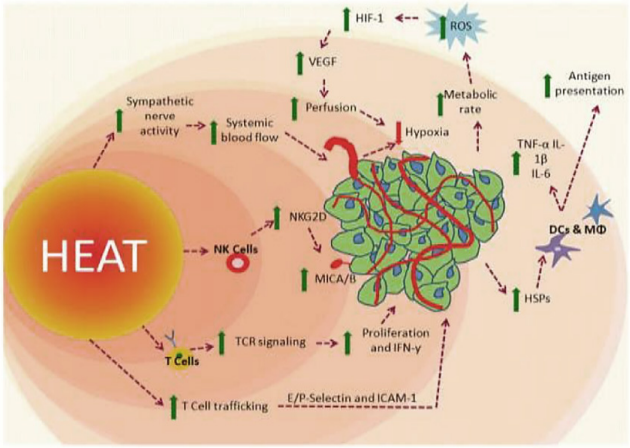

Figure 6 Schematic Targeting based on temperature change [33].

Active targeting

Active targeting by interfacing receptor-targeting atoms to a sedate conveyance framework permits the medicate to be conveyed particularly to tumor tissues, cancer cells, subcellular organelles or other atoms particular particles in cancer cells. This approach targets medicate transporters to surface carbohydrates, receptors and particular antigens within the target tissue and is particularly critical within the treatment of essential tumors that have not metastasized (**Figure 7**) [33,34].

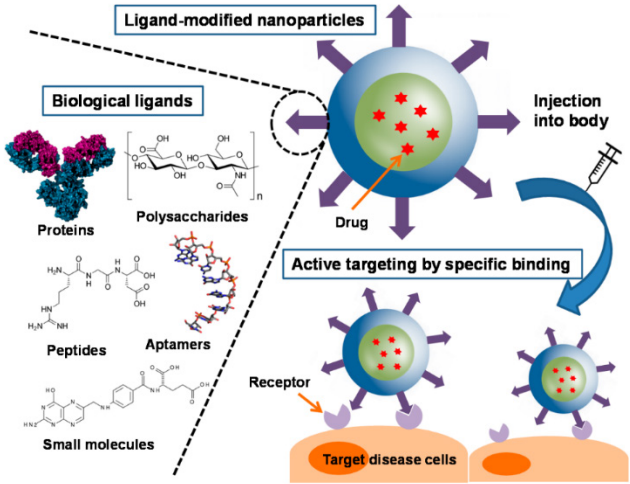

Figure 7 Schematic active targeting [33].

Targeting against carbohydrates

An illustration of dynamic focusing on is the carbohydrate lectin framework. Cell surface carbohydrates impact the intuitive of tumor cells with sound body cells and the extracellular lattice [34-36]. These intuitive happen through proteins called lectins that have the capacity to tie to carbohydrates. A few lectins can distinguish diverse carbohydrate designs on cancer cells as "remote" designs and trigger natural and versatile resistant reactions. Ponders have appeared that lectins play a vital part in tumor cell survival, connection to the endothelium and extracellular network, and tumor angiogenesis [37-40]. These intelligent can be misused to make focused on sedate conveyance frameworks by official to carbohydrate ligands (coordinate lectin focusing on) or by official to lectins (invert lectin focusing on) (**Figure 8**).

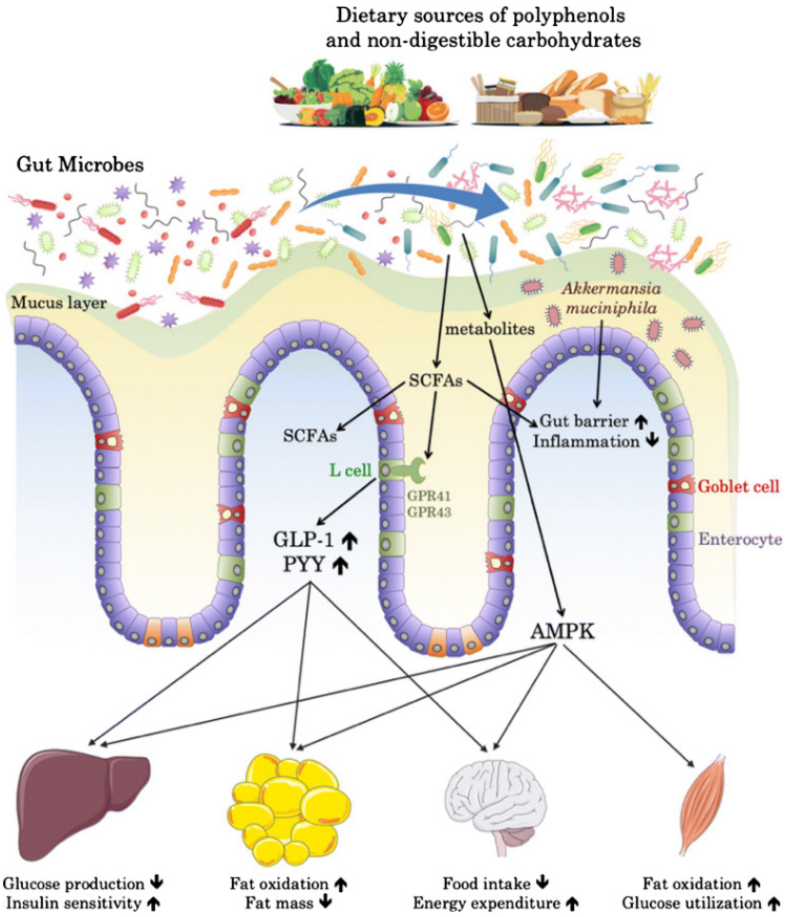

Figure 8 Schematic targeting against carbohydrates [33].

Targeting against antigen and receptor

Tall expression of antigens and receptors in cancer cells gives a course for calm systems to enter through endocytosis [40,41]. Drugs bound to polymeric carriers enter cells through receptor-ligand brilliantly [42,43]. The Drug can be confined from the polymer by lysosomal proteins inside the extracellular space, on the cell surface, and especially interior the lysosomes (**Figure 9**).

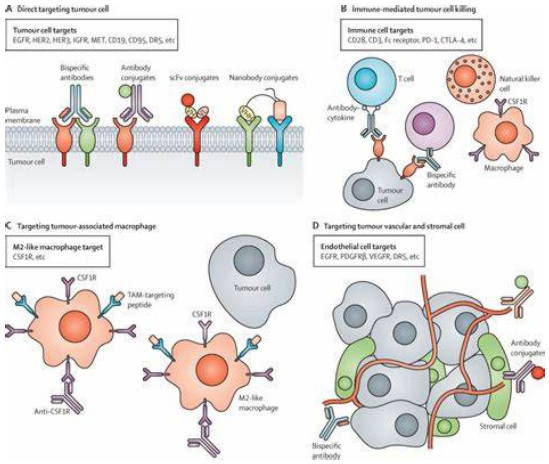

Figure 9 Schematic targeting against antigen and receptor [33].

Monoclonal antibodies

Monoclonal antibodies are the primary and most viable gather of receptor-targeting particles with the capacity to tie to particular tumor antigens. The improvement of antibodies against cancer depends on the distinguishing proof of the suitable antigen, which is communicated on the surface of all cancer cells but not on sound cells. Rituximab was affirmed by the FDA (World Nourishment and Medicate Organization) in 1997 for the treatment of B lymphoma. Another counter acting agent utilized to treat breast cancer is trastuzumab. This counter acting agent ties to the Her2 receptor, which is exceedingly communicated in roughly 20 - 30 % of ladies with breast cancer. Later therapeutic nanotechnology inquire about has centered on utilizing antibodies to target chemotherapy drugs to cancer cells by conjugating these antibodies to the surface of pharmaceutical Nano frameworks. For illustration, rituximab and trastuzumab have been conjugated to nanoparticles containing polylactic corrosive. This focusing on increments nanoparticle section into cells by 6 times (**Figure 10**) [45].

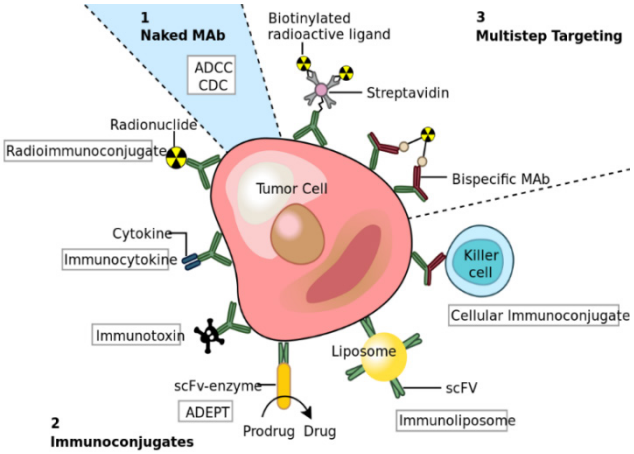

Figure 10 Schematic monoclonal antibodies [45].

Aptamers

A modern bunch of receptors focusing on atoms is aptamers. Aptamers are oligonucleotides made from RNA or DNA that receive a particular spatial shape that gives them the capacity to tie to ligands through intramolecular intelligent. Aptamers can be fabricated to tie particularly and with tall liking to target antigens such as antibodies.

Preferences of aptamers over antibodies as focusing on particles [46]:

To begin with, exceptionally diverse ligands are recognized, such as aptamers, particles, cellular metabolites, vitamins, infections, and different drugs such as ibuprofen. Aptamers can moreover recognize stereoisomers of distinctive atoms such as caffeine and theophylline. Moment, aptamers with tall partiality for target atoms can be produced within the research facility employing a strategy called orderly advancement of exponentially enhanced ligands (**Figure 11**) [46].

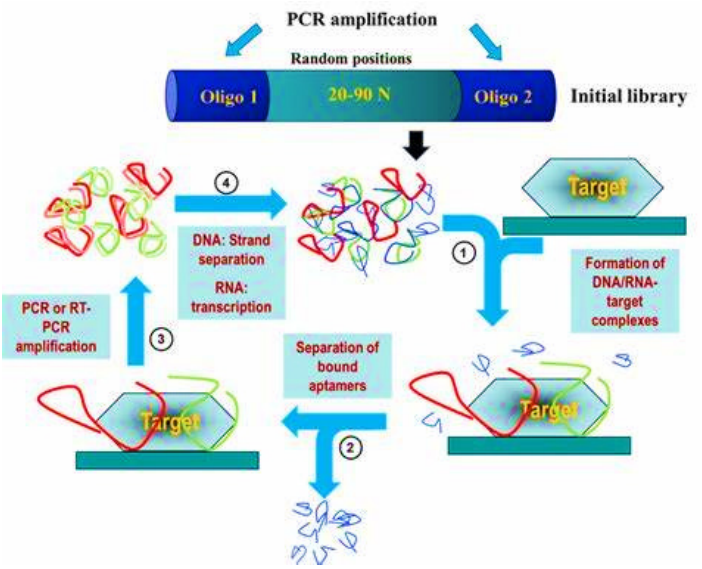

Figure 11 Schematic aptamers [46].

Oligopeptides

The use of peptides as receptor targeting molecules has become increasingly important in recent years. The advantages of peptides over antibodies are their small size, low immunogenicity, high stability, and ease of production. These peptides include the arginine-glycine-aspartic acid tripeptide (**Figure 12**) [47].

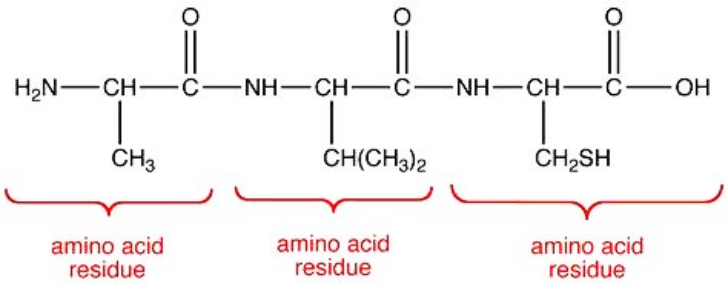

Figure 12 Schematic oligopeptides [47].

Folate

Folic destructive (folate) is one of the preeminent basic and as regularly as conceivable utilized centering on particles. The folate receptor is exceedingly communicated in various sorts of cancer, checking breast, uterine, lung, brain, and colon cancers. Folic destructive ties especially to the folate receptor. This centering on particle was conjugated to diverse sorts of steady carriers, tallying liposomes, polymeric nanoparticles, and dendrimers. In any case, this receptor to boot appear in

normal epithelial cells of the stomach related framework, lung, kidney, placenta, and choroid plexus, so these systems require help think around (**Figure13**) [48].

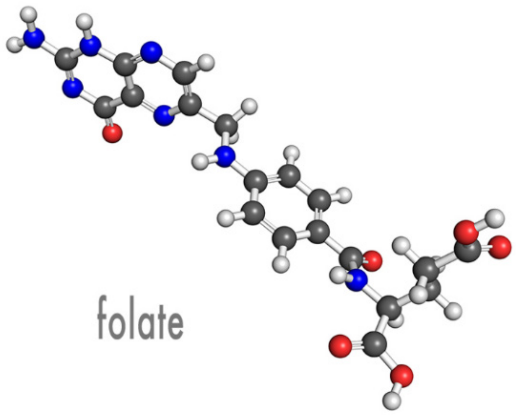

Figure 13 Schematic folate [48].

Types of nanoparticles

A wide range of forms, sizes, and materials make up nanoparticles used for medication administration. These structures exhibit diverse capacities for drug loading, release, cell targeting, and stability [49].

Dendrimers

Dendrimers are regularly tree-like 3-dimensional structures with a central atom (**Figure 14**). Branches can be included to the central portion by polymerizing or synthesizing the central particle [49-51]. The branches have estimate confinements, eventually making a little but overwhelming circular shape. Sedate particles can be joined to utilitarian bunches on the surface of the tree or set between the tree branches. Dendrimers may contain both hydrophilic and hydrophobic particles. Ordinarily, the hydrophobic center encompasses a depth that can oblige the hydrophobic sedate [52]. Hydrophobic drugs have not been of much intrigued, but there has been investigate into the detailing of a few hydrophobic drugs, such as methotrexate, in hydrophobic media (**Table 1**).

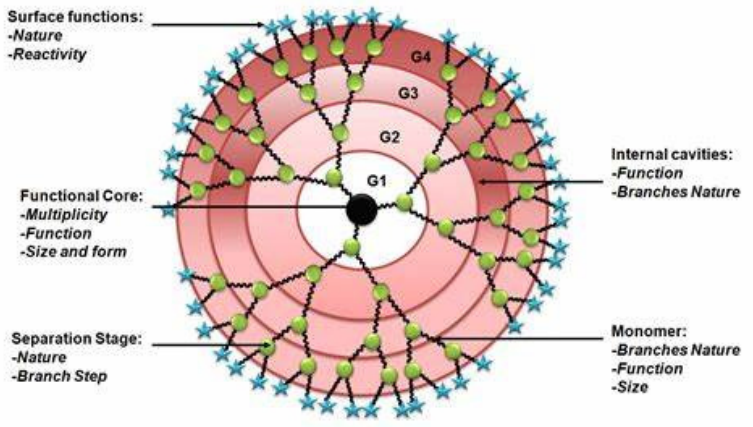

Figure 14 Schematic dendrimers [51].

Table 1 Researches carried out on Dendrimers to load anticancer drugs [51].

Drug	Formulation	Research phase
Doxorubicin	Dendrimer-like polylysine	*in vitro*
Methotrexate	Dendrimer-like polypropylene imine	*in vitro*
Methotrexate	Dendrimer-like polypropylene imine	*in vitro*

Nanospheres

These nanoparticles are spherical matrix structures in which drugs are fully dispersed (**Figure 15**). The surface of these structures can be modified by adding polymers or biological materials such as ligands or antibodies that are used for targeted drug delivery [52].

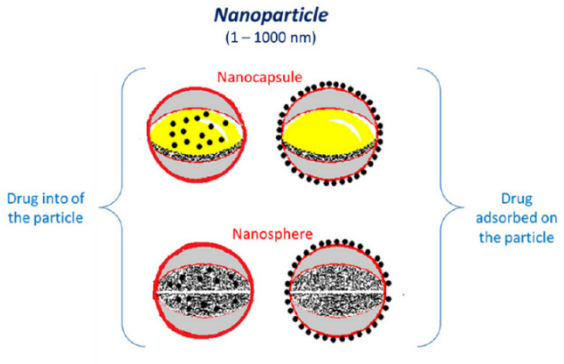

Figure 15 Schematic nanospheres [52].

Nano capsules

These structures are spherical systems in which drugs are placed in the empty center. The center, which can be an oily or liquid medium, is covered with a polymer coating (**Figure 16**). Ligands or antibodies can be placed on these polymers to target drug delivery. The compound in the center of this structure can be a solid, liquid, or gas [52].

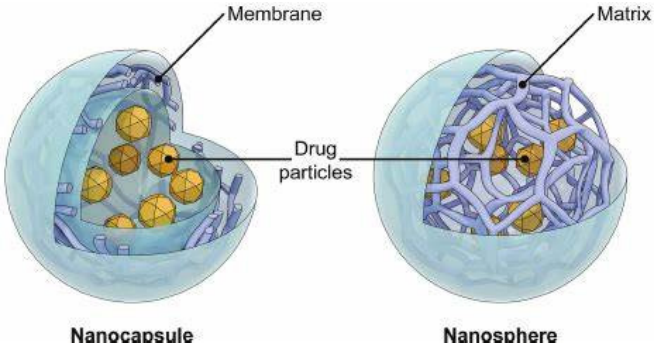

Figure 16 Schematic nanospheres [52].

Liposomes

These structures are closed vesicles consisting of 2 lipid layers, and are divided into unilamellar and multilamellar groups depending on the number of lipid layers. The central unilamellar system is wet and can accommodate water-soluble drugs, while the multilamellar structures can accommodate lipid-soluble drugs. Targeted drug delivery using liposomes is also possible. H. Ligands or antibodies can be attached to the surface of these structures. External energy such as

ultrasonic energy, homogenization, stirring, and heating are often used to generate these particles [51,52].

Loading of drugs into liposomes can be done in 2 ways. First, the drug is dissolved in an aqueous solution and then added to the lipid phase. This process results in multilamellar liposomes. Second, unilamellar liposomes are first prepared and then an aqueous solution of the drug is added. In this case, the drug passively passes through the liposomes until the cavity is saturated. The removed drug is then separated from the liposomes by dialysis, chromatography columns, or centrifugation [50]. Depending on their structure, liposomes can be loaded with water-soluble drugs in their hydrophilic portion and hydrophobic drugs in their lipophilic portion. In this way, 2 or more drugs can be loaded simultaneously into liposomes and used for multiple treatments. Due to this property, liposomes are most commonly used to manufacture nanoparticles (**Figure 17**). **Table 2** also lists some research and clinical procedures that are performed using liposomes.

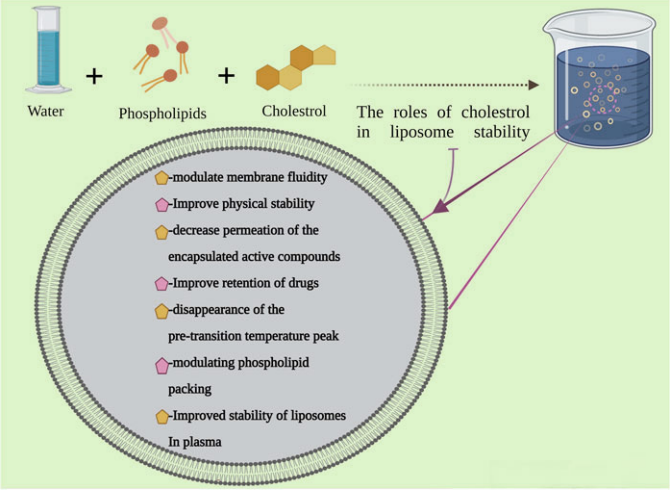

Figure 17 Schematic structure, biomedical applications liposomes [52].

Table 2 Drug-containing liposomes and clinical stages of pharmacology [52].

Drug	Clinical stages
cytarabine and daunorubicin	Phase II
irinotecan and cisplatin	*In vivo*
mercaptopurine and daunorubicin	*In vitro*
quercetin and vincristine	*In vitro*
Doxorubicin and verapamil	*In vitro*

Micelles

Micelles are spherical or globular structures that consist of 2 hydrophobic parts in the middle and a hydrophilic part around it. These structures are suitable for the transfer of hydrophobic drugs as the drug deposits in the central part, which is also hydrophobic. One type of micelle is the polymeric micellar nanoparticle, which has made great advances in drug delivery to tumors (**Figure 18**) [53].

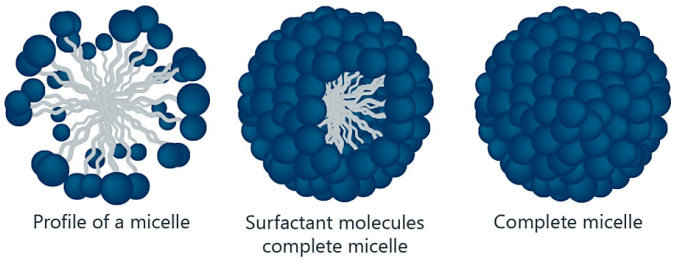

Figure 18 Schematic micelles [53].

Polymer micelles

A number of Food and Drug Administration (FDA) approved polymers are used to manufacture polymeric nanoparticles (**Figure 19**). These structures are more stable and have a smaller size range compared to liposomes. The release of active ingredients through these particles is also easier to control. Amphiphilic polymers are often used to manufacture nanoparticles. Active ingredients can also be loaded into these particles using various methods [50-53]. Drugs can get into nanoparticles during manufacturing. For example, in nanoprecipitation techniques, a water-miscible solvent such as acetonitrile is used to dissolve the hydrophobic drug and/or amphiphilic copolymer. Nanoparticles are then created by mixing this solution with water and evaporating the solvent with water. In another method, first a chemical bond is created between the drug and the polymer and then this conjugated polymer can be used for the preparation of nanoparticles. By optimizing the surface of the polymer, it can also be used for therapeutic purposes. Micelles are also considered as one of the suitable options for loading multiple drugs due to their ambidextrous nature. **Table 3** shows some of the polymers used for the preparation of nanoparticles and the type of host on which the experiments were performed.

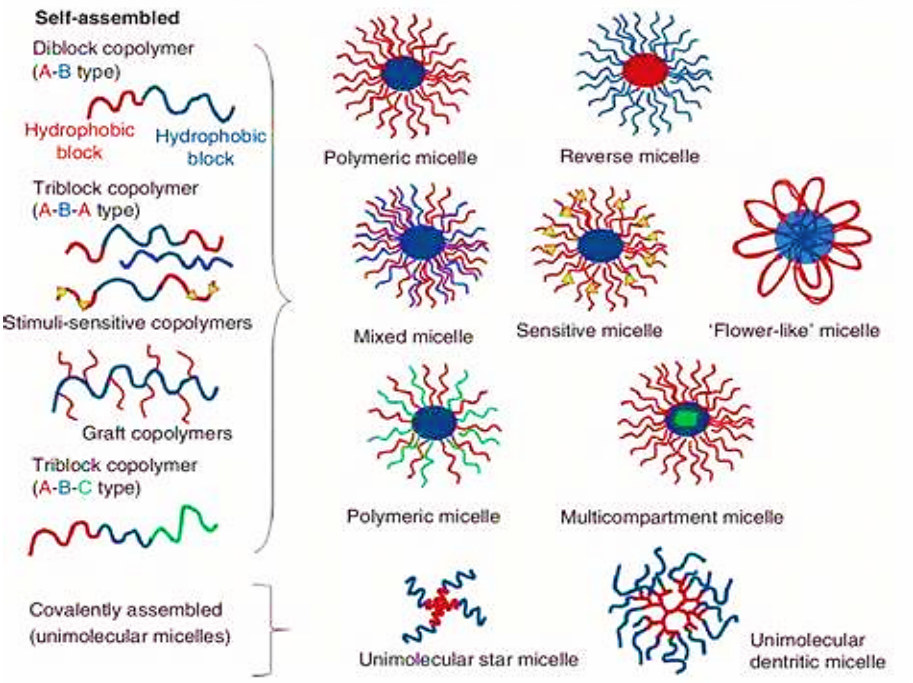

Figure 19 Schematic polymer micelles [53].

Table 3 Drug-loaded polymeric nanoparticles and host types tested [50].

Drug	Polymer	Experiment
Doxorubicin	PLGA, PIBCA, Albumin, PAMA	Mouse, Rabbit, Human
Methotrexate	PBCA	Mouse
5-fluorouracil	Albumin, PGL	Mouse
Paclitaxel	PVP	Mouse
Dactinomycin	PHCA, PIBCA	Mouse
Irinotecan	PLA, PPG	Mouse

Worm-like micelles

These structures are cylindrical polymeric micelles that are used as a new kind of carrier. These micelles are only micrometers long, but can slip through tiny holes like worms. By loading drugs into these structures and modifying their surface, they have been used to deliver drugs to tumors. Lipophilic drugs can also penetrate the worm-like micelles (**Figure 20**) [54].

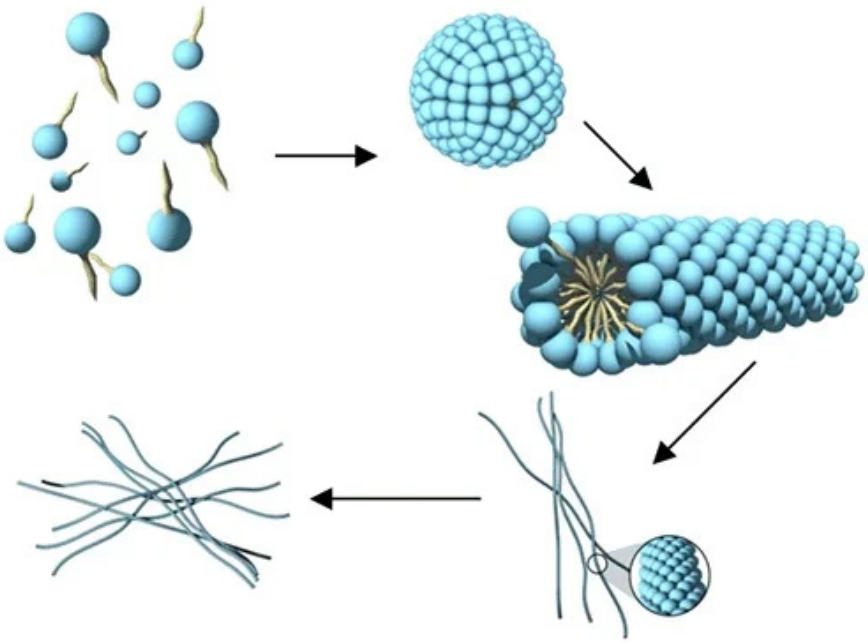

Figure 20 Schematic worm-like micelles [54].

Fullerenes and nanotubes

These structures are carbon molecules in the shape of hollow spheres or tubes (**Figure 21**). Spherical fullerenes, also known as buckyballs, resemble soccer balls. Carbon nanotubes are cylindrical fullerenes that can be single-walled or multi-walled. Drugs are delivered into these structures and antibodies or ligands are placed on their surface [54].

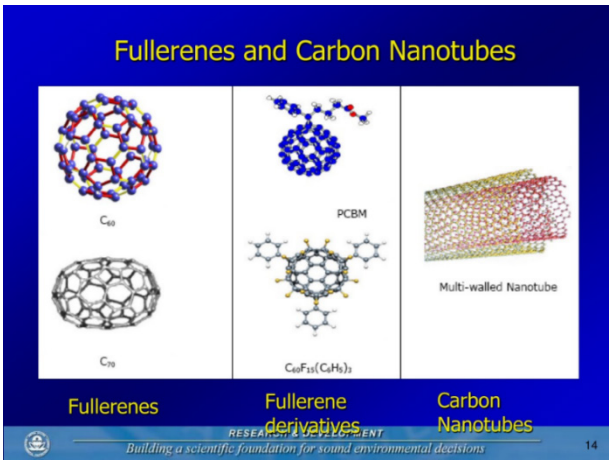

Figure 21 Schematic fullerenes and nanotubes [54].

Polymerases

Polymerases are comparative to liposomes, but that they are composed of amphiphilic polymers/peptides and take the frame of a round structure (**Figure 22**). These structures are steadier and more adaptable than liposomes. Polymersomes frame suddenly when the copolymers are hydrated. The thicker the copolymer, the longer the sedate will stay within the body [52].

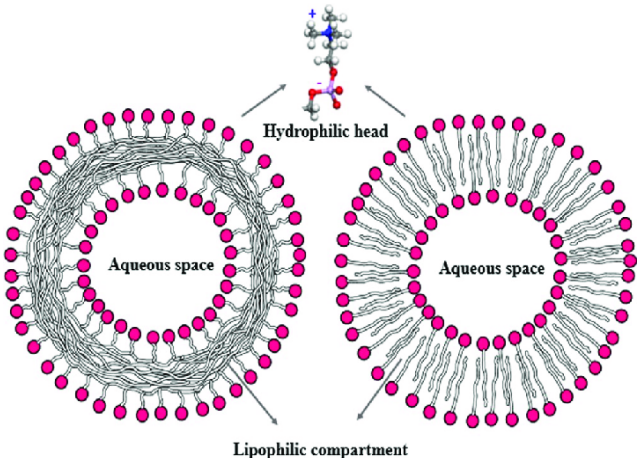

Figure 22 Comparison of the structure of polymersome and liposome [52].

Surface modification

After receiving an intravenous injection, lipophilic nanoparticles are quickly removed from the circulation by macrophages, which then transport them to the liver or spleen. Although this might be seen as a benefit when targeting the liver, it is important to consider the impact of macrophages when aiming to transport medications to other parts of the body. Additionally, medication binding to blood proteins is an issue with drug delivery. As a result, less medication is accessible to the cancer cells as there is less free medicine in the circulation. A class of optimized carriers known as stealth carriers has been created to address these issues. Hydrophilic polymers such as polyethylene glycol (PEG = polyethylene glycol), polysaccharides, poloxamines, and poloxamers are used as surface modifiers for these structures [50-52]. These compounds may be mixed with other ingredients by chemical bonds during production. Nanoparticles or surface absorption enter the overall structure of the particle. The presence of these compounds arranges a cloud of neutral and hydrophilic chains on the surface of the particle, protecting the nanoparticle from proteins and

macrophages. These nanoparticles have a long half-life and release the active ingredients in the body for a long period of time [53,54].

Targeted nanoparticles

Nanoparticles may connect to certain cell receptors and transport medications to particular cells by attaching ligands to their surfaces, as already discussed in the preceding section [55,56]. **Figure 23** shows a schematic representation of targeted medication delivery in action, showing how antibodies attached to nanoparticles bind to certain antigens on tumor surfaces. The overarching objective of targeting and surface optimization of nanoparticles is to lessen medication-induced adverse effects while increasing the likelihood of drug delivery to tumor cells. Researchers have also looked at using magnetic nanoparticles as a means of delivering drugs specifically to tumor areas. In this method, nanoparticles containing magnetically active substances such as Fe_3O_4 are first generated and then guided to the desired tissue through an external electromagnet [57-59]. These particles are also called inorganic nanoparticles. In this way, the drug reaches the desired tissue precisely. These structures are often not useful on their own and are used in combination with other structures such as polymers. When specific ligands are attached to these particles, they can be used for targeted drug delivery. Of course, this type of nanoparticle was tested on surface tumors in animals, but in some cases the high doses of drugs that reached the target cells destroyed them (**Figure 24**).

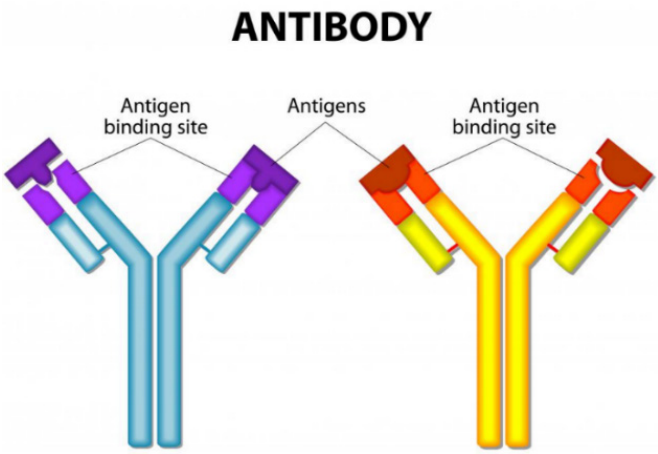

Figure 23 Binding of antibodies present on the nanoparticle surface to specific antigens on the tumor surface [56].

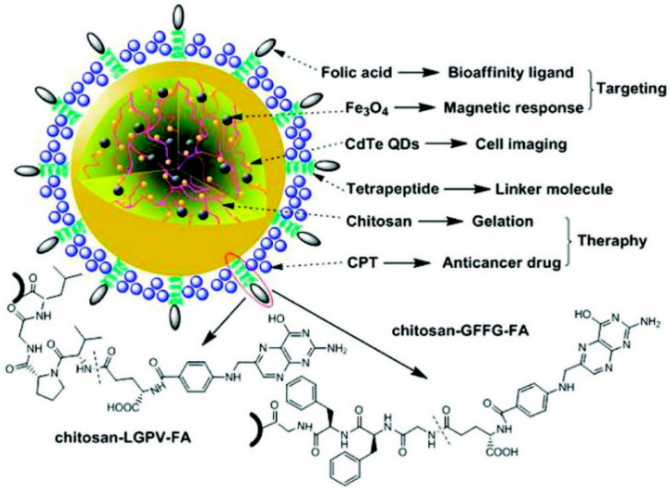

Figure 24 Iron nanoparticles and polymers for targeted drug delivery [55].

Commercialized products

Cancer remains one of the world's deadliest diseases today. It is estimated that more than 1.5 million new infections and more than 500,000 deaths were reported in 2010. Remarkable advances have been made in the field of cancer biology, which has greatly helped to gain insight into the fundamentals of the disease. However, translating basic cancer biology understanding into clinical practice remains a challenge. Despite progress in the development of cancer therapies, it is becoming increasingly evident that cytotoxic chemotherapy will remain the mainstay of cancer treatment. However, current chemotherapy involves nonspecific drug delivery, which results in adverse side effects with toxicity and often limits its potential. This requires a paradigm shift in treatment with the development of novel therapeutic strategies. Over the past 2 decades, nanotechnology-based approaches have emerged as an exciting field that promises to address this limitation by extending half-lives and improving targeting efficiency. These advantages are made possible by several parameters including their size, their enhanced permeability and retention (EPR) effect allowing their implantation into the tumor, their ability to evade the immune system and thereby improve drug half-life, their significantly reduced effective dose 50 (ED50) and their potential for selective targeting due to their high surface density. For these reasons, nanotherapeutics are becoming a new paradigm in cancer research. **Table 4** shows the drugs available in the pharmaceutical market. Typically, these drugs use nanoparticles as carriers [54].

Table 4 Types of commercially available anticancer drugs and their carriers [54].

Drug	Product name	Carriers
Daunorubicin	Daunoxome	Non-pegylated liposomal
Doxorubicin	myocet	Non-pegylated liposomal
Doxorubicin	Doxil/caelyx	pegylated liposomal
Platinum	prolindac	polymer
Paclitaxel	abraxane	Albumin nanoparticles
Asparaginase	oncaspar	Polymer-protein nanoparticle
Paclitaxel	Genexol-pm	Polymer micelle
Paclitaxel	Nk105	micelle
Asparaginase	Nk911	micelle

Polylactide-co-glycolic acid (PLGA) nanoparticles

The copolymer of polyglycolic acid (PGA) and polylactic acid (PLA) is called polylactic-co-glycolic acid (PLGA). It is created by the ring-opening polymerization of glycolide (GA) and lactide (LA). When it comes to medication delivery, PLGA has various benefits as a biomaterial. The first is that it is safe for human usage; both the FDA and the EMA have given their stamp of approval [41]. Second, compared to many natural polymers, it is pure, has a more adjustable molecular weight, and is easier to reproduce since it is a synthetic polymer. Thirdly, PLGA breaks down naturally. In the body, hydrolysis produces lactic acid and glycolic acid, which are processed by the Krebs cycle into carbon dioxide and water [42]. And lastly, the copolymers may be used for long-term, continuous medication release since they are less susceptible to hydrolysis than PLA and PGA.

Fabrication of PLGA nanoparticles

Emulsion evaporation method

A typical method for creating PLGA nanoparticles is emulsion evaporation [43]. If the medicine is water-soluble, one of 2 emulsification techniques may be used. In order to encapsulate hydrophobic pharmaceuticals, a single emulsion (oil-in-water, o/w) is appropriate, however a double emulsion (water-in-oil-in-water, w/o/w) is more appropriate. A single emulsion approach involves

dissolving PLGA polymer and hydrophobic drug in an organic solvent, followed by the addition of water and a surfactant to the organic phase to create an emulsion. To keep the emulsion droplets from sticking together, it's common practice to utilize high shear forces, including sonication or quick stirring [41-43]. Next, the organic solvent is evaporated or extracted to eliminate it. Then, the nanoparticles that have been created may be recovered using centrifugation (**Figure 25**) [44,45]. Double emulsions are created by modifying the aforementioned technique for the purpose of encapsulating hydrophilic medicines. A first emulsion is made by combining an organic solvent with a water solution; the second emulsion is made by adding the first combination to a water solution that already contains a stabilizer. The emulsion evaporation technique works well for making PLGA nanoparticles in a controlled environment, but it's not practical for mass manufacturing. Rapid homogenization and sonication need a large amount of energy, which is the primary cause [45]. There are a few drawbacks to using double emulsion evaporation to create nanoparticles, such as: B. The medication loading efficiency is poor and the particle size is large.

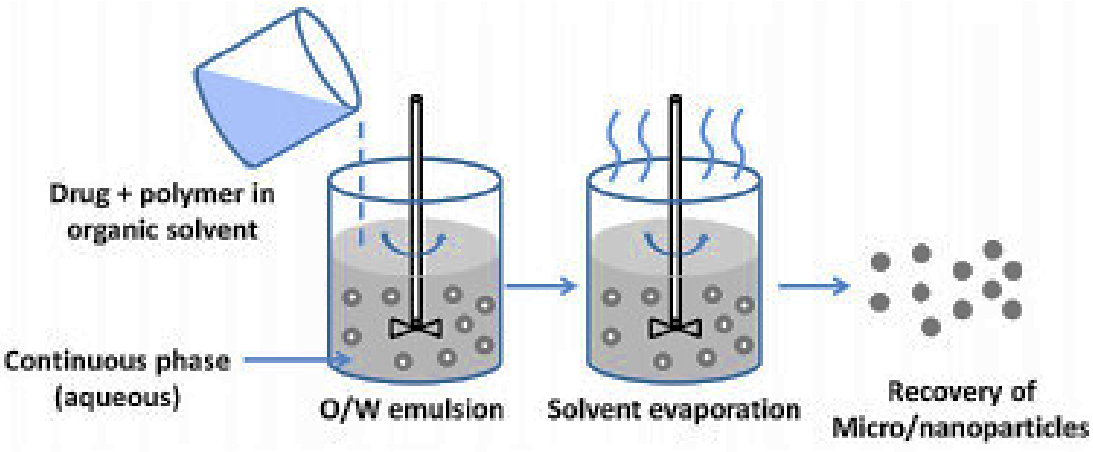

Figure 25 Fabrication of nanoparticles by emulsion evaporation method [25].

Salting out method

The salting-out process involves dissolving PLGA in an organic solvent, such acetone, that is water-miscible in order to create PLGA nanoparticles. The next step is to quickly agitate an aqueous phase that contains an emulsifier and a high salt concentration (e.g., calcium chloride) before adding the polymer solution. Diluting the salt concentration speeds up the organic phase's migration into the water phase, which in turn induces the creation of PLGA nanoparticles. Centrifugation or cross-flow filtering is used to remove the salt and organic solvent (**Figure 26**). Encapsulating peptides or proteins is a good fit for the salting-out approach since it lowers tension forces [47]. Because nothing has to be heated during the procedure, it is perfect for encasing medications that are sensitive to heat [48]. One disadvantage of this approach is that it requires an extra washing step to remove salts, and it can only encapsulate hydrophobic active substances [49,50].

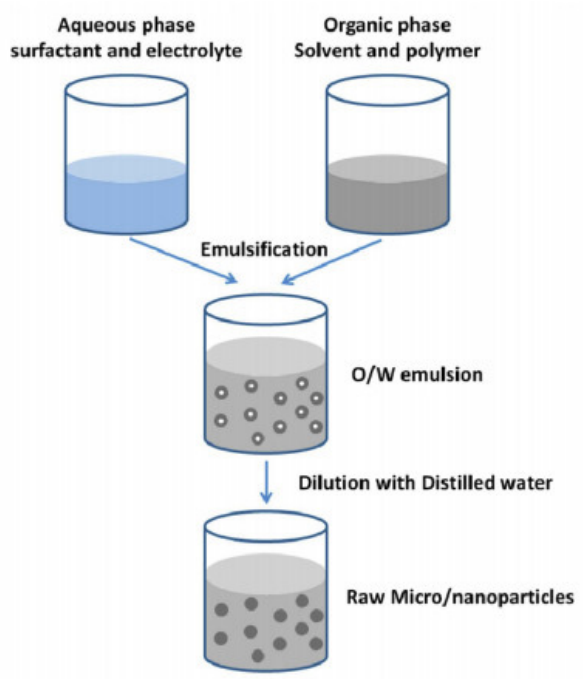

Figure 26 Fabrication of nanoparticles by emulsion evaporation method [25].

Applications of PLGA nanoparticles in cancer treatment

The majority of PLGA nanoparticle uses include active targeting techniques for the administration of chemotherapeutic medications in cancer therapy, while passive delivery via the EPR effect is shown to be inadequate for tumor delivery of nanomedicines. The surface of PLGA nanoparticles is often coated or grafted with targeting ligands. Cancer cells and tumor endothelial cells often overexpress certain receptors, which the chosen ligands bind to selectively [107-109].

An appropriate targeting component for PLGA nanoparticle DDS in cancer therapy is hyaluronic acid (HA), a naturally occurring polysaccharide that interacts to the CD44 receptor. This receptor is overexpressed in certain tumor types. In comparison to other targeted ligands, HA has several benefits, including being non-immunogenic, biocompatible, and biodegradable. created PLGA nanoparticles capped with HA to deliver paclitaxel (PTX) to specific areas of triple-negative breast cancer patients. To create PLGA nanoparticles with a positive charge, a single emulsion approach was used to add cetrimide to the water phase. Sodium hyaluronate, which has a negative charge, was added to the surface after the solvent dichloromethane (DCM) had evaporated completely [110]. We looked at how different formulation factors, such sonication duration, polymer concentration, and PVA content, affected the nanoparticles. The researchers discovered that the nanoparticles' size and polydispersity index (PDI) were reduced when the concentration of PVA was increased from 0.5 to 2 %. Particle size was reduced and PTX's encapsulation efficiency (EE %) and drug loading (DL %) were both enhanced by prolonging the sonication period from 1 to 4 min. One hundred mg of a 50:50 PLGA and 2 % w/v PVA mixture produced the optimal formulation with the greatest EE % (90.8 ± 1.5). Nanoparticles modified with 0.05 % w/v sodium hyaluronate have a zeta potential of around −37.5 mV and a size of approximately 250 nm. Studies on the release of PTX from PLGA nanoparticles coated with HA demonstrated a quicker rate of release compared to naked PLGA nanoparticles. The HA coating increases water absorption, which in turn improves the hydrolysis of PLGA, and generates a porous surface on the PLGA nanoparticles. According to the cell viability data, HA-PTX-PLGA nanoparticles had a lower IC50 value compared to PTX-PLGA nanoparticles. This suggests that HA-PTX-PLGA nanoparticles were more efficiently taken

up by cells. This finding might be a consequence of HA interacting with the overexpressed CD44 receptor in MDA-MB-231 cells. Using an outside stimulation, such a magnetic field, to guide nanoparticles to the tumor is another method of active targeting [53,54]. The researchers Vlerken *et al.* [55] created magnetic PLGA nanoparticles with 2 distinct targets in order to combat brain malignancies. Few chemotherapeutic medicines are available for the treatment of gliomas because of the weak blood-brain barrier (BBB). The scientists tackled this difficulty in glioma therapy by developing an MNP/T7-PLGA NP, a dual-functional PLGA nanoparticle DDS. For ligand-mediated active targeting, the human transferrin receptor binding peptide T7 was chosen, and for magnetically regulated targeting, PLGA NPs were imbued with magnetic nanoparticles (MNPs) by means of a single emulsion solvent evaporation technique. Curcumin (CUR) and paclitaxel (PTX) were chosen as nebulizers for tumor treatment. Mice brain endothelial cell line bEnd.3 and human malignant glioma cells U-87 were used in *in vitro* cellular uptake assays. Results from confocal imaging pointed to T7-mediated intracellular delivery as the primary mechanism causing intracellular delivery. Orthotopic glioma mice were administered Cy5-labeled NPs to study the *in vivo* brain targeting impact of MNP/T7-PLGA NPs. IVIS imaging revealed that the brain had the maximum fluorescence intensity for MNP/T7-PLGA NPs + MAG (with a magnetic field) 4 heet al after injection into the tail vein. When compared to groups treated with either free CUR + PTX or no magnetic field at all, the MNP/T7-PLGA NPs + MAG group had the greatest glioma growth suppression and survival rate (100 %) after 35 days [111].

Comparing theragnostic nanoparticles

For therapeutic evaluation, different nanoparticles have different properties, applications, and associated risks and must be carefully evaluated. The choice of nanotechnology depends on the specific application, balancing the importance of safety and efficacy. As shown in **Table 5**, the toxicity of gold nanoparticles varies depending on factors such as size, shape, and surface modification. Iron oxide nanoparticles are widely accepted but require careful surface engineering to address toxicity concerns. A typical misconception is that silica nanoparticles are safe due to surface modification and functionalization [75]. Surface modification of carbon nanotubes is important to address biocompatibility and potential toxicity concerns and mitigate adverse effects. Coatings, surface modifications, heavy metal concentrations, quantum dots, etc., should also be considered to reduce toxicity levels.

Table 5 Comparison of nanoparticles based on their properties, uses, toxicity, engineering, and safety [25].

Types of nanoparticles	Properties	Applications	Toxicity	Modification	Safety considerations
Gold	High surface-to-volume ratio and distinctive optical properties	Noninvasive imaging with chemicals, targeting/imaging moieties, and therapeutic drugs	Toxicity depends on size, shape, and surface modifications	Nanoconjugates for targeted molecular imaging with decreased systemic toxicity.	Reduced toxicity at specific areas and reduced systemic toxicity.
Iron oxide	Used to target tumors using surface ligands.	Targeted tumor imaging and drug delivery vehicle	Non-targeted and antibody size constraints	Ligands/antibodies for tumor targeting, adjusted to improve tumor site accumulation. Improved cancer diagnosis tool	Improved cancer diagnosis tool effective medicine administration using tailored strategy.

Types of nanoparticles	Properties	Applications	Toxicity	Modification	Safety considerations
				effective medicine administration	
Silica	Size and shape control, functionalization for different applications	Implant in surgery, medication administration, imaging agents, sensitive to changes in pH and temperature.	Misconception about perfect safety.	Mesoporous structures for drug storage, functionalization with imaging agents, and thermoresponsive polymers for controlled drug release.	Generally safe but needs careful assessment for specific uses.
Carbon Nanotubes	High aspect ratio and surface chemical functions	Drug delivery, photoacoustic imaging, fluorescence imaging, and photothermal treatment	Concerns about biocompatibility and toxicity	Surface functionalization for biocompatibility, drug and nucleic acid loading, and precision-targeting ligands	Addresses biocompatibility and toxicological problems for clinical usage.
Quantum Dots	Large surface area for drug conjugation, unique optical characteristics.	tumor detection, medication administration, fluorescence imaging, and photothermal treatment.	Potential toxicity concerns	Coatings for safety, conjugation with therapeutic compounds, targetability	Effective at lower doses, fewer side effects with a tailored approach.
Liposomes	Encapsulate hydrophilic and hydrophobic substances.	Drug delivery, encapsulating chemotherapy, diagnostic imaging, and targeted treatment	Possible immunological responses	Surface-modified with ligands, antibodies, or peptides for targeting and encapsulating of imaging agents	High biocompatibility, low toxicity, useful for targeted medication administration.

Natural product-based nanotechnology and drug delivery

According to a report by the World Health Organization (WHO), in developing countries, the basic health needs of about 80 % of the population are met and/or complemented by traditional medicine [142]. Currently, the scientific community is focusing on research into bioactive compounds, their chemical composition, and the pharmacological potential of various plant species in order to develop innovative active ingredients with relatively few side effects compared to existing molecules [5,143]. Plants have long been known as a vast source of medically important natural compounds and continue to provide a rich resource for the discovery of highly effective new drugs. However, the discovery of active compounds from natural sources poses some problems, due to the fact that they are of biological origin, whose composition of metabolites changes under stress. In

this sense, the pharmaceutical industry has decided to join forces in the development of synthetic compounds [143-145]. Nevertheless, the number of synthetic molecules actually available on the market is decreasing day by day, so that research on active ingredients based on natural products is once again gaining attention, despite the hurdles [145,146]. Most of the natural products already on the market, of economic importance and medical potential, are found in higher plants [143,147]. Several drugs are already on the market that also contain natural therapeutic agents in their composition. Their uses and names are as follows: Treatment of malaria (Artemotil® obtained from the herbal medicine plant Artemisia annua L.), treatment of Alzheimer's disease (acetylcholinesterase inhibitor Reminyl® isolated from Galanthus woronowii Losinsk), treatment of cancer (paclitaxel® and its analogues obtained from the plant Taxus brevifolia, vinblastine and vincristine extracted from Catharanthus roseus, camptothecin and its analogues obtained from Camptotheca acuminata Decne), treatment of liver diseases (silymarin from Silybum marianum) [143]. The composition and activity of many natural compounds have already been studied and established. Alkaloids, flavonoids, tannins, terpenes, saponins, steroids, phenolic compounds, etc. are bioactive molecules found in plants. However, in most cases, these compounds have low absorption capacity due to their large molecular size, which makes them unable to penetrate lipid membranes, reducing their bioavailability and efficacy [147]. These molecules also have high systemic clearance, which requires repeated administration and/or high doses, making the drugs less effective for therapeutic use [145]. Scientific developments in nanotechnology may revolutionize the development of formulations based on natural products and produce tools that can solve the above problems that limit the large-scale application of these compounds in nanomedicine [7,145]. The application of nanotechnology techniques in the medical field has been widely studied in recent years [148,149]. They overcome these barriers and allow the use of different compounds and mixtures in the manufacture of the same formulation. In addition, they can change the properties and behavior of compounds within biological systems [7,145]. In addition to providing benefits to compounds in terms of their solubility and stability, delivery systems can guide compounds to specific sites, increase bioavailability and prolong the action of compounds, combine molecules with different degrees of hydrophilicity/lipophilicity [7]. There is also evidence that combining delivery systems with natural compounds can delay the development of drug resistance and therefore play an important role in finding new treatments for some diseases that are insufficiently addressed by conventional therapeutic approaches in modern medicine [7,145]. Materials based on natural products can be divided into 2 categories: (1) Those that are specifically delivered to a specific location to treat various diseases [43], and (2) those that are mainly used in synthetic processes [196]. The majority of research is aimed at treating cancer, since it is currently the leading cause of death worldwide. Since cancer affects various organs of the body, the development of alternative drugs that specifically combat cancer cells has become a top priority for modern researchers. However, numerous nanomedicine applications for other conditions are also being investigated. These delivery systems are classified according to surface charge, particle size, size distribution, shape, stability, encapsulation potential and biological effect, which can be further used if necessary [33]. Some examples of biological compounds obtained from higher plants and their use in the nanomedicine field are shown in the **Figure 27**. The pharmaceutical industry is constantly striving to develop and apply new technologies to improve existing medicines as well as to further develop and develop modern medicines [71]. In this sense, the accelerated development of nanotechnology is facilitating the development of new formulations through various approaches, such as: delivery of drugs to the site of action (nano-pharmacies), imaging and diagnostics (nano-diagnostics), medical implants (nano-biomaterials), and the combined diagnosis and treatment of diseases (nano-therapeutics) [71]. Many of the nanomedicines currently under development are improvements on drug delivery (AI) systems already used to treat patients. This type of approach examines whether the sustained release of these AIs alters their pharmacokinetic profile and biodistribution. In this

context, Nano formulations may offer advantages over existing formulations if the AIs are targeted to the target tissue, have increased cellular uptake/absorption, and have a lower toxicity profile to the organism. In this section, we focus on berberine, curcumin, ellagic acid, resveratrol, curcumin, and quercetin [8]. Other compounds mentioned include doxorubicin, paclitaxel, and vancomycin, which are also derived from natural products. Nanoparticles have been synthesized using natural products. For example, nanoparticles of metals, metal oxides, and sulfides have been reported to be synthesized using various microorganisms, including bacteria, fungi, algae, yeast, etc. [150] or plant extracts [151]. In the first approach, microorganisms supporting the synthesis process are prepared in a suitable growth medium, mixed with metal precursors in solution, and incubated to form nanoparticles intracellularly or extracellularly. In the second approach, plant extracts are prepared, mixed with metal precursors in solution, and further incubated at room temperature or boiling temperature for a certain time or exposed to light as an external stimulus to initiate the synthesis of nanoparticles. Currently, these natural product-based materials are considered as important ingredients in the production and processing of new Nano formulations, as they have interesting properties such as: B. Biodegradable, biocompatible, available, renewable, and low toxicity. In addition to the above properties, most biomaterials are chemically modifiable, which guarantees them unique and desirable properties for potential applications in the field of nanomedicine [45]. Gold, silver, cadmium sulfide, and titanium dioxide with different morphological properties have been synthesized using a series of bacteria, namely, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, and Klebsiella pneumoniae. These nanoparticles, especially silver nanoparticles, have the highest potential among all metal nanoparticles and therefore have been extensively studied in vitro for their antibacterial, antifungal, and cytotoxic potential. In the case of microbial-mediated nanoparticle synthesis, the research mainly focuses on how microorganisms degrade metal precursors to produce nanoparticles. All these nanocarriers have been formulated to deliver drugs based on natural products. For cancer treatment applications, Gupta *et al.* [152] tested chitosan-based nanoparticles loaded with paclitaxel (Taxol) derived from Taxus brevifolia and used them to treat various types of cancer. The authors concluded that the nanoparticle-loaded drug had superior activity compared to pure paclitaxel with sustained release, higher cellular uptake, and lower hemolytic toxicity [152]. Berberine is an alkaloid from the barberry plant. Chang *et al.* [153], a heparin/berberine complex was developed to enhance the inhibition of H. pylori growth while reducing the cytotoxic effect in infected cells [153]. This is shown in **Figure 28**.

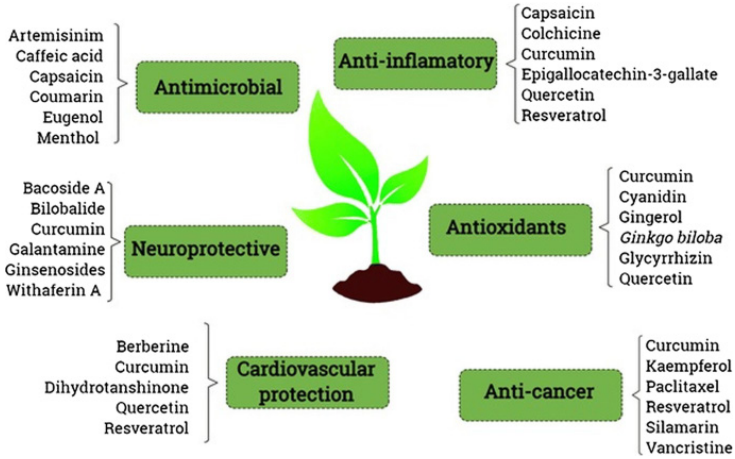

Figure 27 Examples of natural substances obtained from higher plants used in nanomedicine for various purposes. Some of these extracts are already commercially available, others are in clinical trials, others are being extensively studied by the scientific community [154].

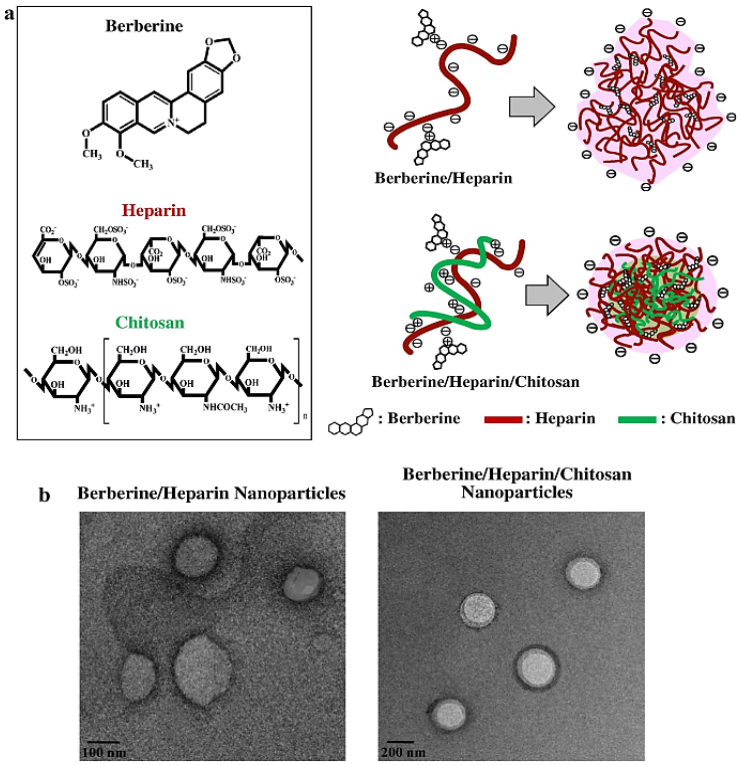

Figure 28 (a) Structures of berberine/heparin-based nanoparticles and berberine/heparin/chitosan-based nanoparticles. (b) TEM images of berberine/heparin-based nanoparticles and berberine/heparin/chitosan-based nanoparticles [154].

Current status and future outlook

The use of nanoparticles in therapeutic applications combining diagnostic and therapeutic functions holds the potential for personalized medicine. However, this innovative approach faces challenges, especially with regard to biocompatibility and toxicity issues associated with the use of nanoparticles in therapy. **Table 6** lists some of the advantages and disadvantages of different nanoparticles in cancer therapy. A major concern is the possibility of adverse biological reactions to nanoparticles, which may lead to unexpected outcomes such as immune responses and inflammation [111]. Achieving optimal biocompatibility remains a challenge, as factors such as size, surface charge, and composition affect the interaction of nanoparticles with biological systems. The challenge is to optimize these elements to minimize immunogenicity. Concerns about long-term toxicity have arisen, especially in therapeutic applications requiring frequent nanoparticle injections, raising questions about cumulative effects [112,113]. Biodistribution, influenced by physiological factors such as pH, can affect nanoparticle stability and behavior, influencing their interaction with biological tissues. Finding a balance between successful targeting and off-target effects is an ongoing challenge, since removal of nanoparticles from the bloodstream by the reticuloendothelial system shortens their circulation time and can impair diagnostic and therapeutic efficacy [114-115]. Achieving multifunctionality adds complexity in diagnostic applications, where nanoparticles play a dual role in imaging and therapy. The balance between imaging and therapeutic potential is difficult, and the choice of MRI, CT, and other imaging modalities can affect overall biocompatibility [116]. Overcoming these issues requires a thorough understanding of the interactions of nanoparticles with biological systems. To improve the overall biocompatibility of nanoparticles, surface modifications such as biocompatible coatings are being investigated by researchers [116]. Advances in nanotoxicology and new testing techniques are essential to properly analyze the safety profile of sensing nanoparticles before clinical implementation. Besides, the

incorporation of nanoparticles into established therapeutic techniques in medical research is promising but comes with challenges and limitations that require a comprehensive understanding [16]. Achieving optimal synergy between nanoparticles and standard therapies requires tailoring factors such as time, dose, and sequence of administration. This integration is complicated by the diversity of biological systems, necessitating precision medical techniques customized to patient profiles and disease characteristics [117]. Concerns regarding side effects and unexpected interactions highlight the importance of understanding the pharmacokinetics and biodistribution of nanoparticles when combined with standard therapies [5]. In addition, potential immune responses and toxicity raise safety concerns, highlighting the importance of comprehensive preclinical and clinical evaluation. Despite these challenges, ongoing research efforts aim to address limitations by leveraging advances in nanotechnology, materials science, and interdisciplinary collaborations to advance integrative strategies to realize the full therapeutic potential of nanoparticle-based and conventional therapeutic interventions combined [117]. For the successful clinical implementation of Nano therapy as a cancer treatment, it is paramount to consider regulatory aspects and address the safety of nanoparticles [118].

As nanoparticles become increasingly important, regulatory authorities around the world are working intensively to develop rules and standards for their safe and effective use [119]. The Food and Drug Administration (FDA) currently plays a leading role in regulating nanotechnology products in the United States, including products that can use nanoparticles to fight cancer [120]. The FDA uses a risk-based approach when deciding whether to use nanomedicines. Precautions to ensure the safety and effectiveness of the product are based on the characterization and toxicity assessment of the nanoparticles. Thus, the classification process of nanotherapeutics as to whether they are considered drugs, biologics, or medical devices requires different selection criteria, as each of these groups is unique [121]. The National Institutes of Health (NIH) and the National Cancer Institute (NCI) also support research into the safety and effectiveness of nanoparticle-based cancer therapeutics through separate funding initiatives. These organizations fund experiments to study nanoparticle toxicity, distribution in the body, pharmacokinetics, and clinical implementation of the substances used in treatment [122]. Globally, national agencies such as the European Medicines Agency (EMA) and the International Organization for Standardization (ISO) are promoting the establishment of standardized protocols and guidelines regarding nanoparticle safety. These activities aim to harmonize regulations in different regions and to facilitate the acceptance and approval of new nanotherapeutics worldwide. Besides, an ongoing effort to minimize the risks of nanoparticle-based cancer treatments is to implement comprehensive preclinical screening procedures [123]. Preclinical testing standards allow researchers to obtain more accurate predictions about the safety profile of nanotechnology-based therapeutics [124] and identify potential risks at an early stage of the development process [5]. Additionally, researchers are applying computer modeling and simulation methods to biological systems to show how nanoparticles function and determine their potential toxicity [125]. Using *in silico* simulations of different nanoparticle formulations, researchers can rapidly identify the most effective candidates and shortcomings of failed drug treatments without the need for extensive resources [126]. Regulatory obstacles and the fact that efforts to certify nanotherapeutic strategies in cancer treatment are ongoing pose challenges to the ability of cancer treatments to move into translational medicine [127]. Researchers can achieve this goal by creating comprehensive regulatory frameworks, preclinical studies, and computer-based models. This will enable researchers to significantly reduce the risks and side effects associated with nanoparticle-based cancer treatments. Besides, studies plan to accelerate the development of this type of cancer treatment and promote its application in clinical trials [5]. Nanotechnology holds promise for personalized and predictive cancer treatment, representing a shift from traditional methods. Predictive oncology aims to use genetic and molecular markers to forecast disease progression and to use a patient's molecular tumor profile

for detection, diagnosis, and treatment [128]. Current cancer treatment options include invasive surgery, radiation, and chemotherapy, all of which can damage healthy tissue and may not eliminate all cancer cells [129]. Nanotechnology may be able to improve radiation-based treatments by enabling direct surgical removal of tumors and facilitating targeted drug delivery to cancer cells and neoplasms [130]. In clinical research, nanotechnology not only facilitates drug delivery but also facilitates the development of new drugs with the unique properties of nanomaterials [131]. The physical properties of nanoparticles, such as energy absorption and back-emission, can be used for applications such as thermal and laser ablation to destroy diseased tissues [132]. Nanoparticles serve a dual purpose because they contain both radionuclides and active medicinal ingredients and are large enough to accumulate at cancer sites. Nanoparticles functionalized with ligands such as DNA or RNA strands, peptides, aptamers, and antibodies can actively change their destination *in vivo* [133]. Moreover, nanostructured materials have been creatively used to construct immune-stimulating material depots and artificial antigen-presenting cells *in vivo* for long-lasting antitumor activity [134]. These applications lay the foundation for therapeutic, multimodal treatments and efficient drug delivery [57].

Targeted delivery of anticancer drugs to tumor tissues is a promising application of nanotechnology in clinical settings, where this approach aims to improve pharmacokinetics and minimize systemic toxicity associated with chemotherapy [135]. Nano-sized carriers, prepared by encapsulating or attaching chemotherapeutic drugs to the surface of nanoparticles, may significantly improve the overall therapeutic index of a particular drug through Nano formulations [136]. Researchers are working on nanomaterial delivery systems to make chemotherapy more effective while reducing side effects, and even developing photodynamic therapy specifically for leukemia and other myeloid cancers [137]. Nanoparticle-based carrier systems, such as mechanically deformable particles and synergistic approaches to mesoporous silica nanostructures [138], have proven effective in penetrating physiological barriers and targeting specific tumors. Besides, nanotechnology-based research has improved the potential of radiation therapy by exploiting the unique properties of nanoscale materials. The basis of many nanotechnology platforms developed for radiation therapy lies in the interaction of X-rays with nanoparticles, driven by the inherent capabilities of materials at the atomic level. Enhancement of the photoelectric and Compton effects using high atomic number nanoparticles can increase the efficacy of conventional radiotherapy while minimizing negative side effects [120]. Another treatment that benefits from external electromagnetic radiation is photodynamic therapy (PDT), an effective cancer treatment for superficial malignancies. This activates photosensitizers at the tumor site, which then release lethal reactive oxygen species [139]. This represents an additional treatment option, especially when cancer cells have acquired resistance to radiation. Certain nanomaterials have demonstrated the ability to act as dual agents, improving both radiotherapy and PDT simultaneously [137]. Besides, nanomaterial-based delivery methods are well suited for innovative therapeutic approaches, especially those using nucleic acids. Nucleic acids are subject to increased instability due to degradation and systemic circulation [106]. When DNA- or RNA-based genetic treatments, such as messenger RNA, microRNA, and small interfering RNA, are conjugated or encapsulated in nanoparticles, their half-life is significantly extended. A common target for this therapy is the so-called “untreatable” cancer proteins [138]. Researchers are investigating the possibility of using nanotechnology-based nucleic acid delivery devices to treat various types of cancer. They focus on the development and characterization of spherical nucleic acids as carriers of RNA therapeutics for brain tumor treatment [139]. Moreover, in the treatment of vemurafenib-resistant melanoma, polymetformin nanoparticles are used for siRNA delivery, effectively alleviating drug resistance [140].

The science of nanomedicine is currently one of the most fascinating research fields. Extensive research in this field over the past 2 decades has already resulted in 1,500 patents registered and dozens of clinical studies completed [141]. As outlined in the various sections above, cancer

seems to be the best example of a disease where both diagnosis and treatment have benefited from non-medical technologies. By using different types of nanoparticles to deliver precise amounts of drugs to affected cells such as cancer/tumor cells without disturbing the physiology of normal cells, the application of nanomedicine and nano-drug delivery systems is certainly also an upcoming trend. It will remain a future research and development area for the coming decades. The examples of nanoparticles shown in these communications are not uniform in size. Some can actually be measured in the nanometer range, while others are in the sub-micrometer range (100 nm or more). Further areas of research will include further work on materials with more consistent uniformity and better drug loading and release capabilities. The review also highlights major advances in the use of metal-based nanoparticles for diagnostic purposes. The use of these metals, including gold and silver, in both diagnostics and therapeutics is an area of research that may lead to broader applications of nanomedicine in the future. Particularly promising in this regard are gold nanoparticles, which appear to be well absorbed by soft tumor tissue and render tumors susceptible to radiation-based (e.g., near-infrared) thermal therapy for selective removal. Despite an overwhelming understanding of the future prospects of nanomedicine and nano-drug delivery systems, their actual impact on the medical system remains very limited, even in cancer treatment/diagnosis. This is because it is a new scientific field, with only 20 years of real research, and many fundamental properties are still unknown. Fundamental markers of diseased tissues, including key biological markers that allow absolute targeting without altering normal cellular processes, are important areas of future research. Ultimately, nanomedicine applications will advance with increasing knowledge of diseases at the molecular level, or the identification of equivalent-sized markers of nanomaterials or subcellular cells will pave the way for new diagnostics/therapeutics. Therefore, understanding the molecular characteristics of diseases will lead to advances in future nanomedicine applications. Beyond what has been presented in this review using known nanoprobes and nanotherapy products, further research is essential for the broader application of nanomedicine. The concept of controlled release of a specific drug at the affected site, techniques to evaluate these events, the effects of drugs at the tissue/cell level, and theoretical mathematical models of prediction are not yet fully developed. Many studies in the field of nanomedicine have focused on the study of biological materials and formulations, which seem to be in the early stages of their application in biomedicine. The science of nanomedicine is currently one of the most fascinating research fields. Extensive research in this field over the past 2 decades has already resulted in 1,500 patents registered and dozens of clinical studies completed [141].

As outlined in the various sections above, cancer seems to be the best example of a disease where both diagnosis and treatment have benefited from non-medical technologies. By using different types of nanoparticles to deliver precise amounts of drugs to affected cells such as cancer/tumor cells without disturbing the physiology of normal cells, the application of nanomedicine and nano-drug delivery systems is certainly also an upcoming trend. It will remain a future research and development area for the coming decades. The examples of nanoparticles shown in these communications are not uniform in size. Some can actually be measured in the nanometer range, while others are in the sub-micrometer range (100 nm or more). Further areas of research will include further work on materials with more consistent uniformity and better drug loading and release capabilities. The review also highlights major advances in the use of metal-based nanoparticles for diagnostic purposes. The use of these metals, including gold and silver, in both diagnostics and therapeutics is an area of research that may lead to broader applications of nanomedicine in the future. Particularly promising in this regard are gold nanoparticles, which appear to be well absorbed by soft tumor tissue and render tumors susceptible to radiation-based (e.g., near-infrared) thermal therapy for selective removal. Despite an overwhelming understanding of the future prospects of nanomedicine and nano-drug delivery systems, their actual impact on the medical system remains very limited, even in cancer treatment/diagnosis. This is because it is a new scientific field, with only 20 years of real research, and many fundamental properties are still unknown. Fundamental

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Table 6 Advantages and disadvantages of nanomaterials for cancer therapies [25].

Nanoparticle	Advantages	Disadvantages
(TiO_2NPs)	Shows similar cytotoxic effects on cancer cells, generating ROS and causing DNA damage.	Nanoparticles accumulate in RES organs but are cleared through the kidneys before reaching significant tumor levels.
(IONPs)	Capable of guiding uptake through external magnetic stimulation. Can be modified with ligands to improve active targeting for clinical effectiveness.	Active targeting needs significant research to achieve clinical utility
(ZnONPs)	Innately activates pathways, inducing ROS, cytokines, and chemokines, resulting in cancer cell apoptosis. Cytotoxic effects linked to external stimuli like UV light.	In vivo, addressing off-target effects and inadequate tumor accumulation remains crucial.
(AuNPs)	Strong biocompatibility. Proven platform for delivering diverse cancer drugs.	Chemical contaminants from synthesis can cause toxicity issues. Less direct anti-cancer effects than other nanoparticle materials.
(AgNPs)	Good biocompatibility. Directly kills cancer cells.	Size-dependent cytotoxicity requires tuning of particle size. Potential off-target effects with little delivery to the tumor.

Experimental design and methodology

The study established specific inclusion and exclusion criteria to ensure relevance and quality of the sources.

Inclusion criteria

The inclusion criteria focused on selecting original research articles, systematic reviews, and meta-analyses published within the last 10 years, as this time frame reflects recent advancements in nano-based drug delivery. Only articles published in English were considered to maintain language consistency. The articles specifically addressing the tumor tissue characteristics, such as permeability and retention effects, and the targeting mechanisms of nano-based carriers. Full-text access was essential, and only articles available through open-access sources, institutional access, or major databases like PubMed, Scopus, and ScienceDirect were included.

Exclusion criteria

The exclusion criteria eliminated articles that fell outside the scope of cancer applications or did not discuss targeting mechanisms within tumor tissues. Studies older than 10 years were generally excluded to avoid outdated data, except for foundational studies deemed essential for background context. Non-English publications and articles with incomplete data or insufficient methodological details were also excluded to ensure interpretability and quality.

Article selection

Through this selection process, a total of 267 articles were initially screened. Of these, 76 were excluded based on the established criteria, and an additional 37 were rejected after a thorough full-text review. Ultimately, 154 articles met all the criteria and were used as references, providing a solid foundation of recent, high-quality research for this comprehensive review of nano-based drug delivery in cancer.

Conclusions

In recent years, Nano systems for drug delivery have attracted attention. The objectives of the development of these systems, which generally consist of drugs, carriers, targeting ligands and surface modifications, are the controlled release of drugs, the maintenance of drug concentrations within the therapeutic range for an appropriate period of time, and the targeted delivery of drugs to the target tissue. These nanomedicine systems include liposomes, micelles, nanoparticles, antibody conjugates and polymer conjugates that are currently in the clinical stage or have entered the market. In this article, we have briefly reviewed the nature of tumor tissue and the active and passive methods of drug delivery to tumor tissue. Nanostructures have many advantages, such as being able to deliver multiple drugs simultaneously and reducing toxicity to treat cancer cells, so these structures have been able to attract the attention of many researchers. Besides, nanoparticles can be produced using different types of carriers, many of which are approved by the FDA. There are various methods to create these structures. Due to these properties, nanotechnology has created great potential for cancer treatment that can reach from the laboratory to the patient's bedside. The extensive exploration of nanotechnology in cancer diagnostics suggests a potential area for customized treatment. Nanoparticles offer significant advantages in targeted drug delivery, advanced imaging tools and novel therapeutic approaches such as photothermal therapy and controlled drug release. Their ability to target cancer cells while reducing side effects represents a paradigm shift in cancer treatment, but challenges such as biocompatibility, toxicity and integration with existing drugs remain and require further research and development. A future perspective leads to predictive oncology, where nanotechnology may play a key role in early detection, precision treatment and improved cancer outcomes. Nanotheranostics have the potential to transform cancer care by linking diagnostics and therapy, enabling more effective, less invasive and individually tailored approaches.

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