World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Review Article

ROLE OF NANOPARTICLES IN THE TREATMENT OF CANCER: A REVIEW

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Received: 25-10-2024 / Revised Accepted: 11-11-2024 / Published: 19-11-2024

ABSTRACT:

One of the wide variety of diseases known as cancer is characterized by the unchecked growth of abnormal cells that can enter, destroy, and spread throughout healthy human tissue. An unusual lump, unusual bleeding, chronic cough or breathing difficulties, and weight changes, including unintentional gain or loss, are some of the main signs and symptoms of cancer. Currently, traditional cancer treatments are confined to surgery, radiation, immuno, targeted, and chemotherapy, all of which have the potential to be harmful. However, these conventional anticancer treatments, are challenged by drug resistance, severity, and side effects. To combat this, nanotechnology has been the subject of much research and application in the treatment of cancer. This is because nanotechnology possesses inherent anti-cancer properties owing to its antioxidant action, which also inhibits the formation of tumors. When it comes to treating cancer, nanoparticle-based drug delivery offers several benefits over traditional drug delivery, such as improved stability and biocompatibility, higher permeability and retention effect, and precise targeting. Many anti-cancer drugs, such as 5-fluorouracil, methotrexate, Doxil (doxorubicin), and Abraxane (paclitaxel), have been effectively manufactured using nanomaterials. This study summarizes current developments in the field of cancer treatment and addresses the many kinds of nanoparticles, their benefits, and their targeting mechanisms.

Keywords: Cancer treatment, Nanoparticles, cellular targeting, drug resistance

INTRODUCTION

Unwanted, disorganized, and uncontrolled cell division is a hallmark of cancer. Cancer cells, in contrast to healthy cells, never stop growing and dividing throughout their lives to replicate into ever-more dangerous cells. Damage to the DNA (the genetic material within cells that defines cellular features and functioning) of cancer cells is the reason for their aberrant growth and division. Numerous factors can lead to cellular DNA defects and damage. For instance, exposure to tobacco smoke or other environmental variables can set off a series of events that cause cellular DNA abnormalities and ultimately end in cancer. On the other hand, you may inherit faulty DNA from your parents. Tumors are clusters of cancer cells that result from the diseased cells dividing and replicating themselves. Tumors contribute to many of the symptoms of cancer by diminishing, compressing, and destroying the surrounding non-cancerous cells and tissues.

Tumors can be classified as benign or malignant. Benign tumors do not grow and spread as quickly as malignant ones, and they are not cancerous. Benign tumors typically don't represent much of a threat to life. On the other hand, malignant tumors grow and disperse throughout the body as a result of metastasis, the process by which cancer cells move from the site of the original tumor to other body sections.[1]

Approaches for treatment of cancer:

In an effort to eradicate cancerous cells, chemotherapy employs medications that specifically target fast dividing cells. The drugs may have some very dangerous side effects, but they can also help decrease tumors.

Hormone treatment entails taking drugs that prevent the body from producing tumor cells.

Using medications and other therapies, immunotherapy boosts the immune system and aids in the fight against cancerous cells.

Radiation therapy utilizes high-dose radiation to kill cancerous cells.

Individuals who have blood-related cancers, such lymphoma or leukemia, may benefit most from stem cell donation. It means removing red or white blood cells, for example, that have been harmed by radiation or chemotherapy.

A patient's treatment plan usually includes surgery if they have a malignant tumor. In addition, a surgeon may remove lymph nodes to halt or limit the spread of the illness.

Targeted medicines work inside malignant cells to stop them from proliferating. [2]

NANOPARTICLES:

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How to Cite this Article Rama Devi Korni. Role of Nanoparticles In The Treatment of Cancer: A Review. World J Pharm Sci 2023; 12(04): 1-12; https://doi.org/10.54037/WJPS.2022.100905

By connecting medications to custom-made carriers, they can be directed toward specific cells. Numerous nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been investigated as carriers in drug delivery systems.[3] Delivering the therapeutic chemical to the intended site is a major difficulty in the treatment of many diseases. Drugs used conventionally are often used with poor bio-distribution, low selectivity, and limited effectiveness. Controlling the distribution of drugs can help overcome these restrictions and disadvantages. With recent advancements in nanotechnology, nanoparticles—structures smaller than 100 nm in at least one dimension—have shown great promise as drug carriers. Because of their small sizes, the nanostructures exhibit unique physicochemical and biological characteristics (such as an increased reactive area and the ability to pass through cell and tissue barriers), making them a valuable material for biomedical applications. There isn't too much to say about all the possible uses for nanotechnology, but one of its most significant contributions will undoubtedly be to the creation of novel, efficient medical therapies (nanomedicine).[4] Low sensitivity or specificity and drug toxicity are major shortcomings in the existing diagnostic and treatment techniques for several diseases, including cancer. More sophisticated and contemporary methods of cancer diagnosis are being developed based on nanoparticles. They are used as molecular research tools, contrast agents, fluorescent materials, and medications containing specific antibodies. Paramagnetic nanoparticles, quantum dots, nanoshells, and nanosomes are a few of the nanoparticles used in diagnosis. Drugs having a high potential for toxicity, such cancer chemotherapeutic drugs, can be administered with a higher safety profile because to the use of nanotechnology. [5]

HISTORY:

For almost 4,000 years, people have been utilizing nanoparticles without completely understanding the science underlying them. Natural nanomaterials found in many clay minerals have been utilized for thousands of years in fields such as architecture, medicine, and art. In 1857, Michael Faraday conducted research on the production and properties of colloidal suspensions of "Ruby" gold. These unique optical and electrical properties make these some of the most fascinating nanoparticles. Faraday demonstrated how gold nanoparticles can produce solutions with a range of colours under specific illumination conditions. [6] The field of nanomedicines and related nano pharmaceuticals is advancing quickly and becoming increasingly significant in the treatment of cancer. Since 1980, they have been continuously produced and enlisted for commercial objectives in clinical trials. The USFDA approved PEGylated liposomal doxorubicin, also known as "Doxil," as the first nanomedicine in 1995 for the treatment of several types of cancer. Since then, a number of nanomedicine-based nanomedicine-based medications have been developed and commercially marketed. These include nanocrystals, liposomes, micelles, dendrimers, proteins, and metallic-based NP products.[7]

NANOPARTICLES IN TARGETING CANCER CELLS AND OVERCOMING DRUG RESISTANCE:

With the creation of pharmaceuticals based on nanoscale technology, nanotechnology has emerged as a source of novel and inventive medications. Researchers and medical professionals worldwide now find it relatively easier to identify cancer early on and to administer efficient treatment, thanks to a breakthrough in nanotechnology research. Anticipating nano-medicines for cancer treatment and diagnosis is still mostly in the research and development stage. In contrast to traditional chemotherapies, nanotechnology in medicine involves the use of precisely tailored materials to create new therapeutics and technologies that are more effective in precisely targeting pharmaceuticals inside tumor tissue while also reducing toxicity. [8] It has been found that NPs enhance the enhanced permeability and retention (EPR) effect by deeply penetrating tissues. Moreover, the surface characteristics effectively cross the epithelial membrane to affect half-life and bioavailability. For example, nanoparticles coated with the hydrophilic polymer polyethylene glycol (PEG) lessen immune system clearance and opsonization. Furthermore, it is possible to optimize the rate of drug release or active moiety release by modifying the particle polymer's characteristics. Together, these special qualities of NPs regulate their therapeutic effect in the control and treatment of cancer. One of the primary concerns with cancer therapy is managing medication resistance in addition to targeting cancer cells.

It works against all forms of cancer and all treatment modalities. Drug resistance is a phenomenon caused by diseases that become resistant to medicinal treatments. Drug resistance can be divided into two groups: intrinsic and acquired. Innate resistance is usually caused by changes in genes that are already engaged in cell death or proliferation. "Acquired resistance" describes the type of resistance that develops after a certain anti-tumour treatment. The development of novel mutations or modifications made to the tumor microenvironment during treatment may be the cause of this resistance. Nanoparticles can also be used to overcome treatment resistance linked to cancer because of their exceptional ability to co-encapsulate several therapeutic medications .[9]

TUMOR CELL TARGETTING STRATEGIES WITH NANOCARRIERS:

Generally speaking, one needs to functionalize nano-carriers with a range of targeting ligands, including aptamers, proteins, peptides, carbohydrates, and small molecules, in order to target particular tumor cells. These ligands have the ability to selectively bind to overexpressed or tumor-specific antigens or receptors at the cell surface, improving the internalization of the nano-carriers by the tumor cells and extending the retention of tumor tissue. Conversely, a natural biomimetic targeting method has been increasingly popular during the past

ten years. Plasma membranes derived from cancer cells, blood cells, or stem cells may be used to conceal nanocarriers with homotypic or heterotypic sticky properties of source cells for tumor cell targeting.[10]

Due to the tumor's leaking endothelium, nanocarriers are able to enter the vasculature and aggregate in a number of solid tumors. The enhanced permeation and retention, or EPR, effect is what's meant by this. The term passive targeting refers to the combination of this idea with nanocarriers whose surface is designed for extended periods of blood circulation. Targeting ligands can be affixed to the surface of nanocarriers; these ligands bind to particular receptors on tumor cells and endothelium. The delivery of medications is more selective thanks to this active targeting. Utilizing nanocarriers for both passive and active drug targeting to tumors can decrease harmful side effects, boost effectiveness, and improve the transport of therapeutic compounds that are sensitive or poorly soluble. A perfect targeted drug delivery system would passively accumulate the medication within the tissue and shield it first, then actively retain or internalize it.[11]

A tumor is not only a collection of cancer cells; rather, it is a heterogeneous mixture of extracellular matrix, resident and invasive host cells, and secreted chemicals. Through significant changes to the genetic, cellular, and physical characteristics of their host tissues, tumor cells encourage the growth and dissemination of malignancies.[12] The complex ecosystem known as the tumor microenvironment is composed of extracellular matrix, stromal tissue (which includes blood vessels, immune cells, fibroblasts, and signaling chemicals), and cancer cells. Through the release of extracellular signals, the promotion of tumor angiogenesis, and the induction of peripheral immunological tolerance, the tumor can impact the microenvironment. Additionally, the growth and evolution of malignant cells can be influenced by the immune cells present in the milieu. Tumor growth and invasion in healthy tissues are facilitated by the mutual interaction of cancer cells and different elements of the tumor microenvironment. This phenomenon is linked to tumor resistance to existing treatments and a bad prognosis.

Nanocarriers must be able to remain stable in the circulation as long as they reach the target medium (TME) in order to escape being cleared by the reticuloendothelial system (RES) and avoid being sucked up by the mononuclear phagocyte system (MPS). PEGylating the surface of nanoparticles has been shown to improve their hydrophilic qualities and confer stealth features, delaying the immune system's detection of the particles and increasing the likelihood that they will target the intended tissues or cells. to build up in the tumor microenvironment (TME) via atypical tumor vasculature, to enter the tumor's interstitial fluid at high pressure, to reach the active site, and to only interact with the targeted cells. The best way to encourage the accumulation of NPs in the area of interest is by active/passive targeting.[13]

There are two different kinds of targeted drug delivery systems: (I) passive targeted drug delivery, which is based on the enhanced permeability and retention effect; (II) active targeted drug delivery, which is based on ligand affinity to receptors. [14]

Passive Targetting:

The vasculature of the tumor blood arteries is leaky, which facilitates the nanocarriers' easy passage across the endothelium barrier and into the interstitial space. Depending on the type of tumor, the size of the endothelial cell linings can vary from 100 to 700 nm, which is 50–60 times greater than normal endothelium. Moreover, an insufficient lymphatic drainage system leading to insufficient circulation to the extravasated cells in solid tumors results in the build-up of nanocarriers at the tumorous site. The enhanced permeability and retention effect is the name of this process, which is thought to be a helpful tactic for successful tumor targeting. Tumors must successfully carry out EPR for passive targeting to be effective. Additional crucial characteristics of tumors are the pH, angiogenesis, and microenvironment.

Low molecular weight medication nanocarriers are unable to stay at the tumor site for a prolonged time due to the diffusion mechanism; instead, they return to circulation. The targeting behavior of these medications is entirely determined by the pathophysiology and immunochemical circumstances of tumor cells; this is referred to as "passive targeting". In addition to improving medication delivery in the bloodstream, nanocarriers also improve tumor targeting through the EPR effect. Drugs are kept longer in the body by using a range of carriers, such as pH-dependent systems and polymeric materials. Furthermore in favor of passive targeting is the distinct and altered microenvironment around tumor cells in contrast to normal cells. Nonetheless, there are many disadvantages to passive targeting that should not be disregarded, including misconceptions about the EPR effect, variations between animal models and human patients, and limited nanocarrier penetration into the targeted tissues and tumor cells. Several formulations of passively targeted nanoparticulates, such as liposomes, micelles, and polymer nanoparticles, are presently undergoing clinical trials. A selection of the approved formulations is shown in Table 1. [15]

Table 1: Examples of passively tumor-targeted nanocarriers used in clinical settings

Type of nanocarriers	Name(drug)	Indications	Status
Liposomes	Onco-TCS (vincristine)	Ovarian and breast cancer, Kaposi's sarcoma, multiple myeloma (with bortezomib) Non-Hodgkin's lymphoma	Approved
Liposomes	SPI-077™ (cisplatin)	Lung cancer, head and neck cancer, ovarian cancer	Phase II
Liposomes	Caelyx® /Doxil® (doxorubicin)	Ovarian and breast cancer, Kaposi's sarcoma, multiple myeloma (with bortezomib)	Approved
Liposomes	Myocet® (doxorubicin)Onco-TCS (vincristine)	Breast cancer	Approved
Liposomes	DaunoXome® (daunorubicin)	Kaposi's sarcoma	Approved
Nanoparticles or polymer-drug conjugates	Taxoprexin® (paclitaxel)	Various solid tumours	Phase II-IV Phase II-III
Nanoparticles or polymer-drug conjugates	Xyotax® (paclitaxel)	Breast, ovarian, lung cancer	Phase II-III
Nanoparticles or polymer-drug conjugates	Transdrug® (doxorubicin)	Hepatocarcinoma	Approved
Nanoparticles or polymer-drug conjugates	Nanoxel® (paclitaxel)	Advanced breast cancer	Phase I
Nanoparticles or polymer-drug conjugates	Abraxane® (paclitaxel)	Breast cancer	Approved
Polymer micelles	Nanoplatin™ (cisplatin)Xyotax® (paclitaxel)	Breast, ovarian, lung cancer	Phase I-II
Polymer micelles	Genexol® -PM (paclitaxel)	Breast, lung, pancreatic cancer	Phase II-IV

Active Targeting:

A technology that delivers a specific dose of therapeutic or diagnostic material, or both, to a specific ill region within an organ of the body forms the basis of an active targeted drug delivery system.

Drug-loaded nanoparticles (NPs) are employed in situations where conventional chemotherapy is not effective in reducing cytotoxicity or the adverse effects of medications on healthy cells and organs. They also help to control the non-specific dispersion of drugs throughout the body. NPs are drug-loaded particles that target cells recognize through particular receptors or antigens. Therapeutically available formulations of chemotherapeutic drug nanocarriers, such as Doxil and AmBisome, show limited drug release at the tumor site due to their remarkable stability. As a result, systemic toxicity and therapeutic efficacy decreased, making it difficult for them to displace conventional chemotherapy drugs. By employing an active targeting strategy, this limitation can be overcome while simultaneously increasing the concentration and bioavailability of nanocarriers at the sites of tumors. Numerous examples of both antibodies and non-antibodies ligands are found in these targeting ligands, which include peptides like RGD, proteins like transferrin, vitamins like folic acid, and aptamers that facilitate the targeted transport of the nanoparticle to certain cells or tissues.

By employing an active targeting approach, the toxicity of long-circulating nanocarriers to healthy cells can be decreased while simultaneously improving targeting specificity. In an actively targeted approach, a targeting

moiety is attached to the nanocarrier surface to bind the particle to the receptors expressed on the surface of the tumor or endothelial cell.The receptor (or antigen) must be uniformly expressed only on tumor cells and not spread throughout the bloodstream for a targeting moiety and receptor pair to work well together. Considerable research has been done on targeting moieties such as aptamers, peptides, monoclonal antibodies, and antibody fragments. Studies that use these ligands for active targeting are demonstrated in (Table 2). Usually, the moieties are grafted onto PEGylated nanocarriers in order to benefit from the stealth properties of the host particles.[16]

Table 2: Examples of systems that are actively targeted and classified according to the nanocarrier type

Type of nanocarriers	Drug	Targeting ligand	Target
Liposomes	Daunorubicin	Transferrin	C6 glioma
Liposomes	Doxorubicin, epirubicin, vinorelbine	Anti-EGRF MAb	MDA-MB-468, U87 glioma
Liposomes	Doxorubicin	RGD-peptide	Murine B16 melanoma
Liposomes	Doxorubicin	Anti-HER-2 MAb	MCF-7/BT-474 breast cancer
Liposomes	Doxorubicin	Folate	Mouse M109, human KB carcinoma
Liposomes	Doxorubicin	RGD-peptide	C26 colon carcinoma model
Liposomes	Oxaliplatin	Transferrin	C26 colon carcinoma model
Polymer and Micelles	Paclitaxel Doxorubicin	Folate	KB human squamous cell carcinoma
Polymer and Micelles	Paclitaxel	RGD-peptide	MDA-MB-435 breast cancer
Nanoparticles	90Y (radiotherapy)	Anti-Flk1 MAb	K1735-M2 and CT-26 tumors
Nanoparticles	Docetaxel	A10 RNA polymer	LNCaP prostate cancer
Nanoparticles	Paclitaxel	RGD-peptide	TLT liver tumor
Nanoparticles	Paclitaxel	iRGD-peptide	Orthotopic BT474 breast cancer and 22Rv1 prostate cancer

EXISTING DRUGS MANUFACTURED USING NANOPARTICLES TO TREAT CANCER:

Researchers have developed several drugs using nanoparticles for the treatment of cancer. Some of them have undergone preclinical and clinical testing and received FDA approval, and many are in clinical trials and development stages. Here are a few examples highlighting how nanoparticles can enhance drug delivery to cancer cells, improving efficacy and reducing side effects compared to traditional chemotherapy (Table 3). [17]

Table 3: Examples of nanoparticles which can enhance drug delivery to cancer cells

Drug Product	Indications	Date of approval by FDA	Active ingredient	Manufacturing organization
Onco TCS	Non-Hodgkin's lymphoma	In clinical phase 1/2	Liposomal vincristine	INEX pharmaceuticals
Mylotarg	Acute myeloid leukaemia	2000	Gentuzumab-ozogamicin	Wyeth-Ayerst
DaunoXome	HIV- related Kaposi's sarcoma	04/1996	Liposome-encapsulated daunorubicin	Gilead Science
Abraxane	Various cancers Metastatic pancreatic cancer	01/2005 09/2013	Albumin-bound TAX nanospheres Nab-TAX in	Abraxis Bioscience, AstraZeneca

			combination with gemcitabine	Celgene
Doxil(Caelyx)	Ovarian/breast cancer	11/1995	PEGylated DOX	Ortho Biotech, Scheringplough
Oncaspar	leukemia	02/1994	PEG asparaginase	Enzon pharmaceuticals
Lipoplatin	Pancreatic/head and neck/breast cancer	In clinical phase 3	Liposomal cisplatin	Regulon
Atragen	Acute promyelocytic leukemia	In clinical phase 2	Liposomal all-trans-retinoic acid	Aronex pharmaceuticals
SPI-77	Head and neck cancer/lung cancer	In clinical phase 3	Stealth liposomal cisplatin	Alza
LEP-ETU	Ovarian/breast/lung cancers	In clinical phase 1/2	Liposomal TAX	Neopharma
Aurimmune(CYT-6091)	Head and neck cancer	In clinical phase 2	TNF-α bound to colloidal AuNPs	Cytimmune Science
DepoCyt	Lymphatamous meningitis	04/1999	Liposomal cytarabine	SkyePharma, Enzon pharmaceuticals
EndoTAG-1	Breast cancer/pancreatic cancer	In clinical phase 2	TAX	Medigene/ SynCore Biotechnology
Genexol-PM	Breast cancer/small cell lung cancer	Marketed in Europe	TAX-loaded polymeric micelle	Samyang
AutoShell	AuroLase therapy of cancer	In clinical phase 1	Gold nanoshells	Nanospectra Biosciences, Inc.
ThermoDox	Hepatocellular carcinoma	In clinical phase 3	DOX	Celsion
Marqibo	Philadelphia chromosome-negative lymphoblastic leukemia	07/2012	Vincristine	Talon Therapeutics, Inc.

VARIOUS NANOPARTICLES APPLIED IN CANCER THERAPY:

The drug delivery system may consist of peptides, polymers, lipids, or inorganic nanocarriers, depending on the carrier. Conventional systems, including liposomes, nanotubes, and micelles—whether functionalized or not—are shown in Figure 1, whereas advanced systems, combine several modalities with various types of biomaterials to provide multimodal functioning are shown in figure 2.

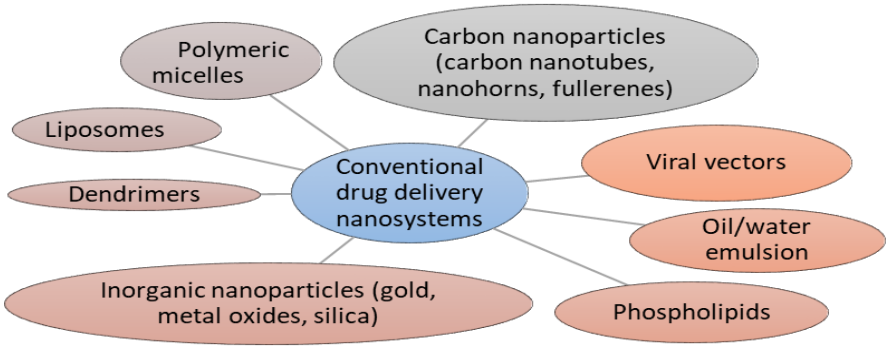

Figure 1: Examples of conventional drug delivery nanosystems.[18]

CARBON NANOPARTICLES:

Due to their distinct biophysical properties, carbon nanotubes (CNTs) are useful for a variety of drug delivery applications. For example, chitosan hybrid nanoparticles (hybrid NPs) and CNTs work together as a vector to deliver methotrexate and enhance anti-cancer activity against lung cancer without causing toxicity to normal cells. In addition, another research group synthesized the AuNPs encapsulating carbon nanotube ring (CNTR) to obtain the highly sensitive PAI-guided cancer treatment.[24] CNTs can also produce heat when exposed to near-infrared radiation, which could be utilized to remove cancerous tissues thermally.[19]

VIRAL VECTORS:

Medical biotechnology and the biomedical sciences have altered viral vectors for a variety of uses. These alterations include their application in oncolytic, vaccines/nanocarriers, medication and gene delivery, and vaccinations.[26] Researchers have been able to produce novel viral mutants with special benefits for therapeutic and diagnostic applications by genetically and/or chemically modifying viruses. Therapeutic chemicals are delivered using these viral vectors. Since human adenoviruses (HAdv) make for up to 50% of viral vectors presently undergoing clinical trial testing, they are especially promising as oncolytic agents and for gene therapy. Furthermore, the delivery of anti-cancer medicines to particular target cells has been demonstrated using different created viruses and viral-like nanoparticles. For example, EGFR-specific (GE11) peptide-loaded virus-like particles made from shrimp nodavirus capsid proteins have shown antigen-dependent transduction in vitro in EGFR-positive cell lines, but not in EGFR-negative control cells.[20]

NANOEMULSIONS:

Nanoemulsions are used for precise drug delivery to targeted areas. They can transport a concentrated amount of chemotherapeutic drugs to cancerous tissues without harming cells and organs in the body's overall circulation. Their efficacy in delivering medication for cancer treatment has been well-demonstrated.[21]

PHOSPHOLIPIDS:

Phospholipids are essential in the treatment of cancer as they target the membrane lipids of cancer cells, enhancing their responsiveness to chemotherapy and aiding in the combat against multidrug resistance. The process hinges on the distinct lipid makeup of healthy cells versus tumor cells, paving the way for tailored therapies that zero in on cancer cell membranes.[22]

INORGANIC NANOPARTICLES:

Because of their unique characteristics, inorganic nanoparticles including gold, metal oxides, and silica are important in the treatment of cancer. The following are some crucial things to think about:

1. **Therapeutic agents**: Due to their distinctive physical and chemical characteristics, adaptability in synthesis methods, simplicity in surface functionalization, and superior biocompatibility, these nanoparticles are being thoroughly investigated as therapeutic agents.[23]

2. **Radiosensitizers**: Certain inorganic nanoparticles can function as radiosensitizers by selectively targeting tumor cells and enhancing the effectiveness of radiotherapy while minimizing damage to healthy cells.[24]

3. **Drug delivery**: Nanoparticles can serve as carriers for targeted drug delivery, which can enhance the immune response against cancer cells and suppress cancer activity.[25]

4. **Hyperthermia treatment**: Because certain nanoparticles may selectively target cancer cells and regulate the release of therapeutic medicines, they are used in the treatment of hyperthermia. One example of such a nanoparticle is superparamagnetic iron oxide nanoparticles or SPION.

These nanoparticles are at the forefront of innovative cancer therapies, providing novel approaches to effectively target and treat cancer.[26]

DENDRIMERS:

Highly branching macromolecules with a star-shaped structure called dendrimers are used in cancer treatment in a variety of ways. They play various roles, including targeted therapy, drug delivery, and antioxidant action.[27]

1. **Targeted therapy:** In targeted therapy, dendrimers can specifically target tumor cells, minimizing damage to healthy tissues. They also regulate the release of anticancer agents within the tumor microenvironment, thereby enhancing the efficacy of anticancer treatments like photothermal and photodynamic therapy.

2. **Drug delivery:** Additionally, dendrimers are used to deliver cancer medications to specific tumors by utilizing the increased permeability and retention (EPR) effect, which lessens the amount of time these medications are exposed to healthy tissues.

3. **Antioxidant action**: Additionally, certain dendrimers, such as polyphenol dendrimers, exhibit antioxidant actions that can be beneficial in cancer treatment.[28]

LIPOSOMES:

Liposomes are spherical vesicles with a phospholipid bilayer; because of their special qualities, they are used extensively in the treatment of cancer.[29] How they help is as follows:

1. **Drug delivery**: By enhancing permeability and retention (EPR) mechanisms, liposomes help medications' pharmacokinetic characteristics. This enables prolonged circulation periods and passive tumor targeting.

2. **Reduced toxicity**: By encapsulating drugs, they may minimize the systemic toxicity associated with free drugs.
3. **Cancer immunotherapy**: The treatment's efficacy is increased by the use of liposomes in both passive and active targeting modes.
4**. Efficacy and side effects**: Liposomal drug compositions may enhance therapeutic efficacy while reducing chemotherapy drugs' deleterious side effects. Liposome technology plays a major role in modern cancer therapy since it allows for targeted distribution with fewer adverse effects. [30, 31]

POLYMERIC MICELLES:

Polymeric micelles are nanocarriers that play a significant role in cancer treatment due to their unique structure and properties.[32] Here's how they contribute:
1. **Drug distribution**: These are efficient methods of distributing anticancer medications that are not highly soluble in water. Their small size and hydrophilic shell allow for prolonged circulation time in the blood and enhanced tumor accumulation.
2. **Targeted therapy**: Studies on polymeric micelles are being conducted as possible uses of nano-medicine in the management of cancer. These micelles can increase body circulation and target certain regions.
3. **Encapsulation of hydrophobic medicines**: Because of their hydrophilic corona, which prolongs blood circulation, hydrophobic medicines might enter tumor tissues through a phenomenon known as enhanced permeability and retention (EPR). Hydrophobic substances may therefore be held within their hydrophobic core.
4. **Tumor imaging and theragnosis**: Therapy and diagnostics are combined in tumor imaging and theragnosis through the use of multifunctional polymeric micelles. A useful weapon in the fight against cancer is polymeric micelles due to their versatility. [33]

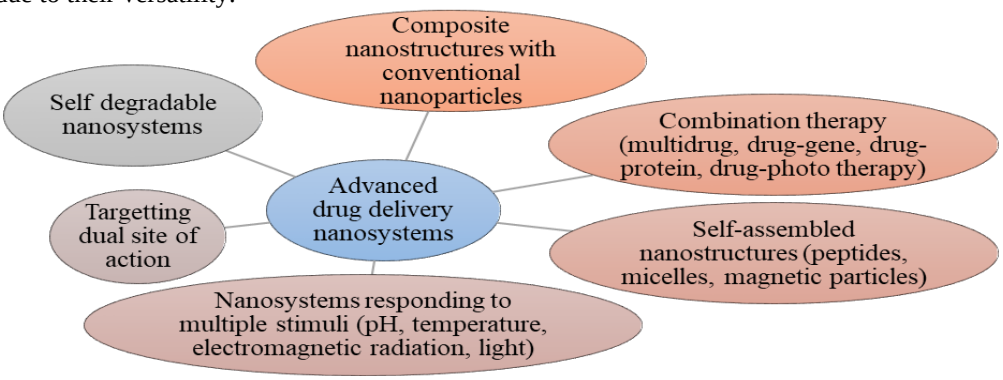

Figure 2: Examples of advanced drug delivery nanosystems [34]

COMPOSITE NANOSTRUCTURES WITH CONVENTIONAL NANOPARTICLES:

In cancer treatment, composite nanostructures made of conventional nanoparticles are crucial.
1. **Gold nanoparticle (GNP) hybrids in multimodal therapy**: GNPs have been hybridized with liposomes and polymers, among other nanocarriers. By combining radiotherapy, photothermal therapy, chemotherapy, and imaging into a single composite device, these hybrids make multimodal therapy possible.[35]
2. **Targeted drug delivery**: Anticancer drugs can be delivered by composite nanostructures. They achieve accurate drug delivery to tumor sites while avoiding systemic toxicity by mixing different types of nanoparticles.[36]
3**. Tumor microenvironment remodeling**: Immune response regulation is significantly influenced by the tumor microenvironment (TME). By means of immune regulation and targeted delivery, engineered nanoparticles transform the TME and improve immunotherapy.[37]
4. **Cancer biosensors biomarkers**: Electrochemical biosensors are produced using nanocomposites such as graphene.
These sensors provide a quick and accurate diagnosis by identifying cancer biomarkers in blood or other body fluids.[38]

COMBINATION THERAPY:

A crucial element of cancer therapy, a medical strategy that mixes two or more therapeutic medications, is the application of combination therapy. In addition to potentially lowering medication resistance, this tactic has therapeutic anti-cancer benefits that include reducing tumor growth and metastatic potential, stopping mitotically active cells, lowering populations of cancer stem cells, and inducing apoptosis. Combination therapy may be able to protect healthy cells from damage while also having cytotoxic effects on cancerous cells. This might occur if one of the combo medications protects normal cells from the negative effects of the other by being less cytotoxic to them. [39]

SELF-ASSEMBLED NANOSTRUCTURES:

Self-assembled nanotechnology has drawn a lot of interest in the medical field because of its low cost, high drug-loading capacity, low toxicity, and easy production method. For many years, NDDS, including polymeric nanoparticles, albumin nanoparticles, dendrimeric macromolecules, liposomes, and inorganic nanoparticles, have been extensively researched as targeted transport carriers for anti-tumor medicines. Peptides, aptamers, and antibodies that have been surface-modified by NDDS can bind selectively to the overexpressed target receptors on the tumor's surface, achieving active targeting of tumor cells in addition to EPR effects. Using NDDS can improve drug loading, increase the solubility of insoluble pharmaceuticals, improve therapeutic targeting to the tumor site, extend the period that drugs are in the body's circulation, and decrease side effects and systemic toxicity. A number of nanomedicines, such as doxorubicin liposomes (Doxil), paclitaxel albumin nanoparticles (Abraxane), and irinotecan liposomes (Onivyde), have been commercialized in recent years for the treatment of cancer. [40]

NANOSYSTEMS RESPONDING TO MULTIPLE STIMULI:

Because they can deliver therapeutic payloads accurately, stimuli-responsive nanosystems are essential to the treatment of cancer.

1.Controlled drug release: These nanosystems are designed to release medication or other therapeutic agents in reaction to particular stimuli. The stimuli can come from the outside (like light or magnetic fields) or the inside (like pH and redox potential).

2.**Personalized delivery**: To reduce their exposure to healthy tissues, nanosystems only react when they come into contact with conditions unique to tumors. *Diminished Adverse Effects*: Regulated medication release amplifies effectiveness while diminishing toxicity.

3.**Illustrations of nanosystems that respond to stimuli:** Albumin Nanoparticles: When the pH of the tumor microenvironment changes, modified albumin-based carriers react. When exposed to light, gold nanoparticles can release medications (photothermal treatment). Targeted medication delivery with magnetic nanoparticles: They respond to magnetic fields.[41]

TARGETING DUAL SITE OF ACTION:

An inventive method of treating cancer that attempts to overcome resistance to targeted drugs is dual-targeted therapy.

1. **Resistance issues**: A lot of malignancies become resistant to current therapies like immunotherapy, radiation, or chemotherapy. Tumor heterogeneity (both intratumoral and inter-tumor variations) brought on by genetic alterations, environmental variables, and other mechanisms are the cause of this resistance.[42]

2. **Dual-targeted therapy (DTT)**: DTT is the process of blocking two or more linked targets or pathways at the same time. These targets may be oncogenic processes or oncoproteins. DTT overcomes resistance to single-targeted drugs by combining parallel or linear inhibition.[43]

3. Benefits of DTT: Enhanced Efficacy: There is a greater likelihood of impacting cancer cells with dual targeting. Overcoming Resistance: DTT gets around some resistance mechanisms by striking several targets. Diminished Adverse Reactions: Targeted medications reduce side effects by sparing normal cells.[44]

SELF DEGRADABLE NANOSYSTEMS:

Self-degradable nanosystems increase the effectiveness of cancer treatment, reduce adverse effects, and improve medication delivery precision. They are quite promising for clinical practice in the future.

1. **Enhanced permeability and retention (EPR) effect**: Liposomes, micelles, and nanoparticles are examples of nanoscale drug delivery systems that employ the EPR effect as a technique. Tumor tissues have poor lymphatic drainage and leaky vasculature, which allows these nanosystems to concentrate preferentially in those tissues due to the EPR effect. This tailored delivery increases drug efficacy while reducing exposure to healthy tissues.

2. **Active Targeting**: Cancer-targeted ligands can be used to functionalize nanosystems. Certain receptors on tumor cells, tumor vasculature, or tumor antigens are recognized by these ligands. Nanosystems can precisely deliver high-affinity and accurate materials to cancer cells by attaching to these targets.

3. **Stimulus-sensitive nanoplatforms**: In a tumor microenvironment, certain nanosystems become sensitive while remaining stealthy in normal circumstances.When they arrive at malignant tumors, certain triggers (pH, temperature, enzymes for example) cause them to discharge their cargo (drugs).

4. **Less side effects**: Drugs are better soluble and protected from deterioration by nanosystems. They enable the use of lower dosages, which lessens harmful effects on healthy tissues.[45]

RECENT ADVANCEMENTS IN NANOPARTICLE-BASED CANCER TREATMENT:

The application of nanotechnology in the biological and healthcare fields has made it possible for physicians to successfully treat patients' problems. Currently, various therapies are used as a wide range of medications. However, the complicated blood vascular structure of tumorous cells, drug resistance, and other pathological features of the cells limit the effectiveness of conventional therapy. Thus, the increasing stature of NPs may

contribute to improved therapy, which is commonly employed as conjugates for liposomes, MNPs, polymeric NPs, etc. [46]

Two things that might affect how well a treatment works are the design of NPs for certain uses and the modification of the pharmacokinetic characteristics. Such nanoparticles require careful consideration of several aspects, making their design a challenging task. The chemistry of the core and the layers must be determined primarily from the structural integrity and stability of the particles in biological fluids. Moreover, physicochemical concerns about the characteristics of the particle, biopharmaceutical concerns about the characteristics of the "bio-barriers," and pharmacological concerns about the location, timing, and duration of the nanoparticles' activity must all be considered during the development process. This process is comparable to that of product drug development. These nanoparticles require new design criteria and must be viewed differently from small and large-molecule medicines. According to the FDA, research on ADME of nanoparticles must be revised to account for their surface chemical properties and tendency to aggregate. [47] Our understanding of nanoparticle biokinetics, metabolism, and clearance is restricted since so few products containing nanoparticles have been clinically investigated.

Lipid- and protein-based DDS make up the bulk of nano pharmaceuticals that the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved for use in the treatment of cancer. Advances in liposome technology, along with the addition of micelles, polymeric nanomaterials, and inorganic-based nanoparticles, along with the use of a wide range of ligands for targeting, have produced a new class of nanopharmaceuticals that are being tested in clinical trials, either on their own or in conjunction with traditional therapies.[48]

Lower dosages of different chemotherapeutic medications can be directed towards cancer cells thanks to the usage of nanoparticles. Furthermore, the administration of many medications to the participants orally is made possible by the use of nanoparticles. Here, anti-cancer drug-laden nanocarriers are loaded with aptamers (RNA nucleotides), nucleolin (DNA nucleotides) aptamers, and epithelial cell adhesion molecules (EpCAM) modified by locked nucleic acid (LNA). This allows for targeted delivery of anti-cancer drugs to cancer cells while preserving normal cells. At the tumor location, remarkably high quantities of drug-loaded nanocarriers ($92 \pm 6\%$) were seen to spread to the cancer cells; normal cells were unaffected both in vitro and in vivo.[49] It is highly anticipated that within the next decade, several NPs with intricate designs will still be utilized at the clinical level, providing therapeutic benefits that traditional NPs cannot offer. In the past, NPs were not used in cancer treatments, but researchers recognized their utility and successfully incorporated them into such therapies. Similar to this, despite though complicated NPs are currently more expensive than their present counterparts, there is a good probability that they will eventually find a permanent home in therapy.[50]

CONCLUSION AND FUTURE PROSPECTIVES:

Researchers from all over the world are looking into nanomedicine as a possible method for effective therapies and medication delivery. Because of their unique benefits, which include improved permeability and retention impact, less toxicity, increased stability, and precise targeting, nanoparticles may be utilized to treat cancer. In the realm of cancer research, nanomedicine holds great potential for the treatment of cancer. One of NPs' special characteristics has been to employ its surface, together with its minuscule size and shape, to play a major part in effective therapy and targeting. Nanotechnology-based treatment and diagnostic approaches present themselves as extremely promising instruments for a quick and affordable cancer diagnosis.

ACKNOWLEDGEMENT

The authors are thankful to Spectrum Pharma Research Solution for providing the Gift Sample, and Niper Hyderabad for Analysing SEM sample.

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