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Review Article

Revolutionizing Cancer Therapy with Nanomaterial

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ABSTRACT

In recent years, there has been a significant advancement in the development of novel drug delivery systems for the treatment of cancer. It has been shown that nanomaterials, which are very effective against cancerous cells, can be developed with special mechanical, optical, electrical, magnetic, and catalytic properties that differentiate them from other dosage forms. Numerous methods of treatment that could be implemented in the healthcare system have been documented, including molecular diagnosis, identification of diseases, nanoscale immunotherapy, and anticancer drug delivery. The purpose of the review is to summarize the scientific data supporting the use of tiny particles conjugated with various therapeutic agents, including carbon nanotubes, liposomes, and gold nanoparticles. This review provides an overview of the drug targeating mechanism, photothermal therapy, photodynamic therapy, and photoacoustic imaging by using carbon nanotubes.

INTRODUCTION

With 7.9 million deaths globally in 2007, cancer was the top cause of death, according to the World Health Organization (WHO). It is anticipated that the number of deaths from cancer would rise globally, to an estimated 12 million by 2030 [1] Cancer is a condition that occurs when certain body cells proliferate out of control and invade other bodily areas. Since the human body is composed of trillions of cells, cancer can begin almost anywhere in the body. Human cells typically proliferate and divide by process known as cell division to create new cells when the body requires them. New cells proliferate and replace old ones when they age or undergo harm. This ordered process can occasionally be disrupted, leading to aberrant or damaged cells proliferation and spreading when they should not. In such condition lump of tissue is form known as "tumour". While Malignant tumor have the ability to metastasize, or spread into, neighbouring tissues and organs. This process allows the tumor to grow into new locations inside the body. Benign tumors are unable to invade or spread to tissue adjacent to

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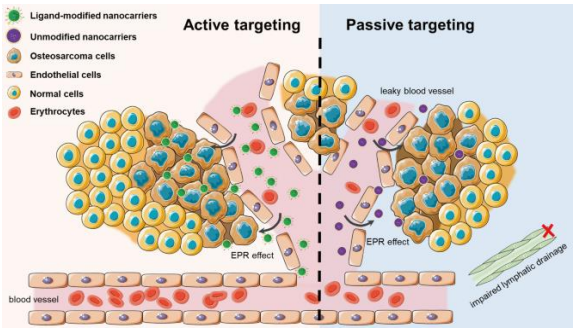
them. So benign tumor rarely grows back after removal, while malignant tumor usually do**.** [2] The traditional approaches for treating cancer include mainly radiation therapy, targeted therapy, immunotherapy, chemotherapy, surgery, and hormone therapy. [2] Unwanted side effects is one of the main consequences of chemotherapy. In order to minimize the harmful effects on healthy cells, much research is therefore done to develop novel therapeutic formulations using particular nanoparticles for targeted administration. [3] The development of materials with dimensions that range between 1 and 100 nm is referred to as nanotechnology. These nanomaterials are distinct from bulk materials in their chemical and physical properties due to their small size. The possibility of developing modern human disease treatments and diagnostic tools is being boosted by the rapid development of nanomaterials research. The National Institutes of Health in the United States has named this branch of nanotechnology used in disease diagnosis, surveillance, and treatment as "nanomedicine" [1]. Various nanostructures, including metal-based nanoparticles, carbon nanotubes (CNTs), quantum dots, liposomes, and gold nanoparticles, are employed in therapeutic and diagnostic applications. The accumulation and release of pharmacologically active drugs at the tumor site can be enhanced by nanoparticles, which can also increase therapeutic efficacy and lessen the severity of negative effects on healthy tissues.

2. Mechanism of drug targeting

2.1 Passive drug targeting

It involves drugs penitration through the tumor vasculature and building up in solid tumors. This process is referred as the enhanced permeation and retention (EPR) effect. Passive drug targeting also relies on the reticuloendothelial system (RES), which is part of the body's immune system and is composed of phagocytic cells that include monocytes and macrophages. [4] [5] [6]



(Fig no. 1 schematic illustration of active targeting and passive targeting of nanodrug delivery system in cancer therapy. [4])

2.2 Active drug targeting

It is the interaction of a drug or carrier with target cells, often through ligand receptors or antibody-antigen acceptance, which leads to intracellular localization. Various biomarkers are specifically expressed or strongly expressed on the surface of cancerous cells, and the ligand-modified nanocarrier system may precisely identify tumor cells by adhering to these biomarkers, resulting in very little damage to healthy tissues. [4]

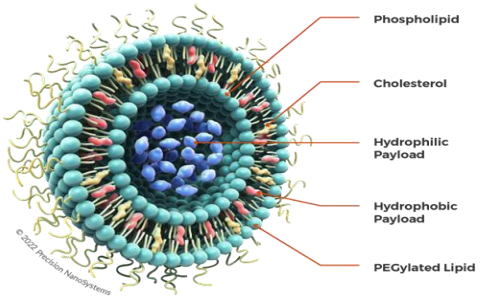
The nanodrug formulation modifies the kinetics, biodistribution, and release profile of the active substances, thus improving cancer treatment and increasing EPR. Drugs target tumor cells by either ‘actively targeting’ or ‘passively targeting’. cell-specific activities or local surroundings, facilitating absorption and accumulation in cancerous tissue and inflammatory regions. The EPR effect causes small nanoparticles to concentrate and invade tumor tissues, bypassing clearance in the spleen. The primary benefit of

these nanostructures is that they promote endosomal escape and ensure cytosolic distribution of the drugs, which leads to an effective biological-based therapy. [3] **.** However, several studies have shown that the transport mechanism can be influenced by nanoparticle physicochemical properties such as size, charge, shape, distinct endocytic machines in different cell types, aggregation state, and surface chemistry.

3. Liposomes

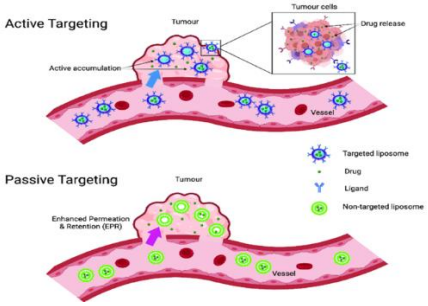
liposomes being among the most established yet still promising drug transporters. They may range in size between 25 nm to 2.5 μm. [7] liposomes precisely deliver synthetic or natural chemotherapeutics (48, 49). They are made up of an aqueous core inside and a phospholipid bilayer outside. 8,50,51 Hydrophobic and hydrophilic medications can be enclosed in liposomes, which are closed spherical vesicles. They may internalize into cells or be liberated via diffusion. Liposomes consist of several hydrophobic tails and hydrophilic heads that are kept in place by surfactants . (fig no. 2) This structure enables the incorporation of lipophilic components between lipid bilayers and the immobilization of hydrophilic components inside. The first liposomal medication authorized by the FDA to treat AIDS patients' kaposi's sarcoma is Doxil, a PEGylated liposomal formulation. [8]

Liposomes can employ both passive and active targeting techniques to specifically target cancerous areas . The primary reason liposomes target tumor tissues passively is that the endothelial cells in the tumor microvasculature have different pore diameters than the "tighter" structures found in normal capillaries. Thus, the optimum targeting goal would be accomplished if liposomes were prepared with a size that permits them to extravasate in tumor tissues while preventing the carriers from leaving the capillaries in normal tissues [7]



(Fig no. 2 structural representation of liposome image taken from [9])

A range of ligands are employed to take advantage of any particular antigens expressed by cancer cells in order to accomplish the active targeting of cancer areas. For example, conjugating RNAA10 onto PLA-block-PEG co-polymers has been successful in targeting the prostate-specific membrane antigen, and this has led to enhanced drug delivery to prostate tumor tissue in comparison to non-targeting nanoparticles.[7]

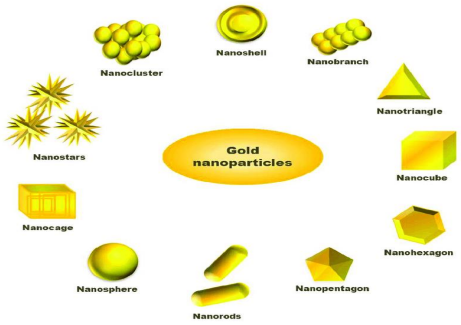


(fig no. 3 schematic illustration of liposomal active and passive targeating [10])

Drug release from liposomes can potentially be enhanced or triggered by external stimuli [146]. Liposomal formulations stable at physiological pH can incorporate pH-sensitive co-polymers; however, these will hydrolysed at acidic pH values of 6 and below, which are frequently observed in the tumor microenvironment. pH-responsive liposomes can be made of poly acrylic acid and poly methacrylic acid [11] . The lack of accessible preparation techniques, the low degree of drug loading stability and capacity, and the rapid disintegration of liposomes in the human body prior to achieving the intended therapeutic impact are some of the main drawbacks of liposomes. [12]

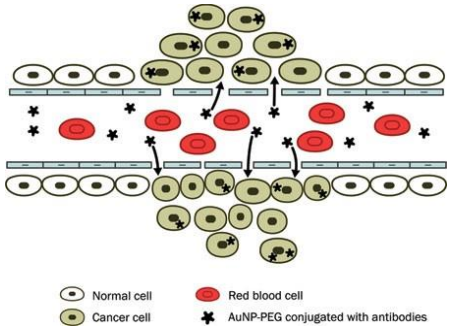
4. Gold nanoparticles

Scientists are interested in using gold nanoparticles as drug carriers due to their optical, tuneable, and surface plasmon resonance (SPR) characteristics. Controlling their distribution is made easier by the wide variety of core diameters (1 to 150 nm) in which they may be developed. The gold nanoparticles' versatile surface is due to their negative charge. This implies that adding different biomolecules, like medications, targeted ligands, and genes, can quickly modify their functions. [13] Since gold nanoparticles have unique structure, surface area, amphiphilicity, carrier capacities, and biocompatibility, they are the main subject of biomedical study. Low cytotoxicity to normal cells, increased blood stream cargo lifespan, easy size control, modified surface chemistry, boosted therapeutic effects, elevated drug incorporation into cancer cells, enhanced pharmacokinetic effects, and optimized biodistribution are all demonstrated by gold nanoparticles [3] . Still, the application of these nanoparticles is restricted due to a number of disadvantages, including low encapsulation effectiveness, poor storage stability, and slow endosomal escape [14] .



(Fig no. 4 Different types of AuNPs, according to their shape and structure. [15])

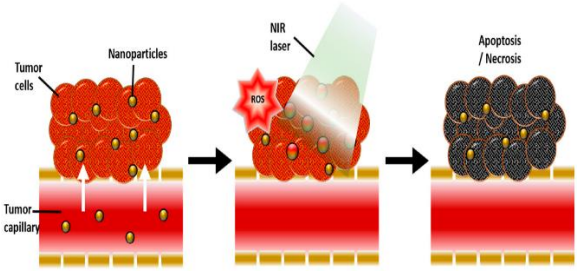
Via forming chemical and physical linkages, gold nanoparticles can be coupled with a variety of small molecules, monoclonal antibodies, or short RNA strands like siRNA and miRNA to create a range of configurations. Once RNA is loaded into Ag nanoparticles, the cancer cell recognizes the genetic code and it become the target for the cancer cell [3] .



(Fig no.5 Build-up of ligand-targeted gold nanoparticles fused with anticancer drugs in cancer cells [16].)

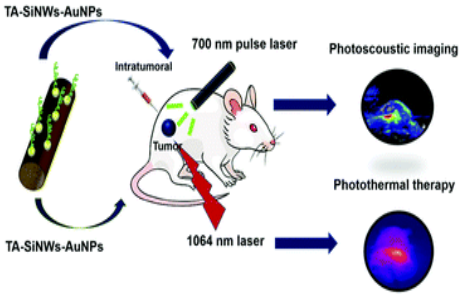
Additionally, owing to the strong visible light interaction, AuNPs are promising candidates for labelling applications. Targeted and accumulated at the exact location of interest, AuNPs allow for visualization of the region under research due to their unique optical scattering capabilities. Phase contrast optical microscopy, dark field microscopy, photothermal imaging, and photoacoustic imaging are among the methods that can be used to identify AuNPs. Furthermore, transmission electron microscopy still favours AuNPs for immuno-staining and imaging at high resolution due to their large atomic weight . [1] [17]

Photon-mediated generation of the localized therapeutic temperature, or photothermal therapy (PTT), may trigger hyperthermic physiological responses. Simply, it melts the tumor into molten gold. This treatment makes use of metal nanoparticles (like gold) that conveniently convert photons into heat and show surface plasmon resonance [48]. Furthermore, the wavelength of plasmonic absorption can be adjusted by fine-tuning the nanoparticles' size, shape, and surface characteristics. The majority of the time, rod- or shell-shaped gold nanoparticles are utilized in PTT [13] .



(Fig no. 6 Diagrammatic representation of the physiological and biological effects of gold nanoparticle-mediated photothermal therapy (PTT) and photodynamic therapy (PDT). [18])

Incorporating light, photosensitizers, and tissue oxygen, photodynamic therapy (PDT) is an additional cancer treatment option. PDT depends entirely on tissue oxygen availability, in contrast to PTT, which is oxygen independent. In PDT, a photosensitizing substance, like porphyrin, is injected intravenously into the tissues and stimulated by particular wavelengths, resulting in the energy transfer that produces reactive oxygen species (ROS) and induces apoptosis in the cells. [13] Millions of functionalized gold nanoparticles are injected into the tumor at a specified location, where they bind to the cancer cells and gets illuminated, thereby making it easier for oncologists to differentiate between the carcinoma and healthy cells. This novel approach to cancer treatment is termed as photoimaging. Because of their bio-inertness and capacity to offer greater spatial and temporal resolution for visualization. The gold nanoparticle including in photoimaging are nanorods, nanocages, and nano shell which are recognized as the best photo imaging nanoparticles currently on the market for cancer therapies [13] [17] .

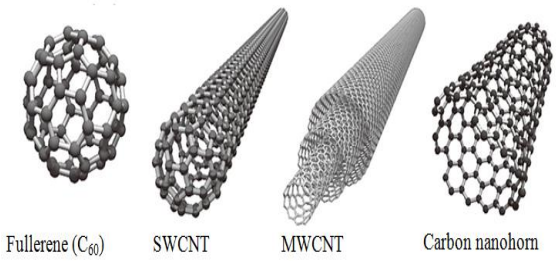


(Fig No. 7 Photoscoustic and photothermal therapy [19])

5. Carbon nanotubes

CNTs firstly discovered by Sumio Iijima in 1991. since they have received a great deal of attention in biomedical fields, carbon nanotubes (CNTs) have such distinctive shapes and characteristics—such as high aspect ratios, huge surface areas, rich surface chemical functionalities, and size stability at the nanoscale—they have drawn more and more attention in the biomedical domain [20] .

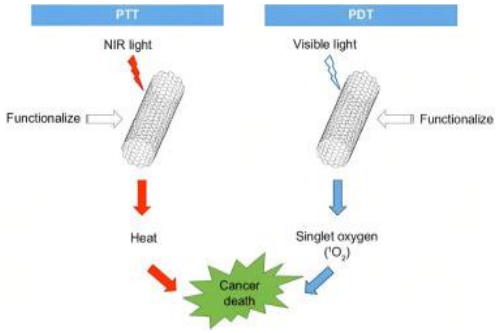
They have particular appeal when used as mediators and carriers for cancer treatment. CNTs have been employed as nanocarriers for genes such as RNA/DNA aptamers, small interfering RNA, plasmid DNA, and, as well as anticancer medications such as paclitaxel, Pt (II), and Pt (IV) through adequate functionalization. Proteins and elements of immunotherapy can also be transported through CNTs. These have also been used as facilitators for photothermal therapy and photodynamic therapy, which use combinations of photons to directly get rid of cancer cells without significantly damaging healthy tissue. [20]



(Fig no. 8 structures of various important carbon nanomaterials: Fullerene (C_{60})

Single-Walled Carbon Nanotube (SWCNT), Multi-Walled Carbon Nanotube (MWCNT) and Carbon Nano horn [21])

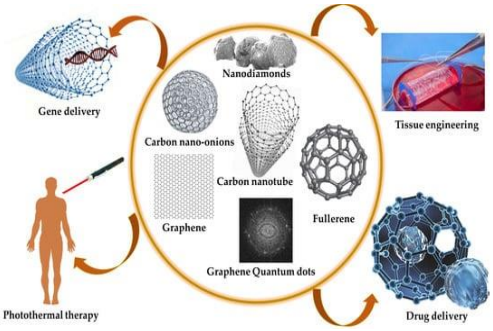
Cancer treatments based on CNTs: Topoisomerase inhibitors, platinum, antimicrobials, and other anticancer chemical carriers are among them. Small interfering ribonucleic acid, aptamers, antisense oligonucleotides, and plasmid DNA are examples of gene carriers. PTT, PDT, and combinations of PTT and PDT are found in carbon nanotube mediators, whereas streptavidin, rich A chain, immune active chemicals, are examples of protein carriers. [20]



(Fig No. 9 Processes of PTT and PDT using CNTs. [20])

Many medications, polypeptides and nucleonic acid, can be incorporated into CNTs because of their distinct ultrahigh surface area. Functional CNTs can cross the plasma membrane of mammalian cells because of a process known as endocytosis. CNTs come in contact with cancer cells, they have the special capacity to recognize the particular surface receptors that can trigger receptor-mediated endocytosis. Considering CNTs have these benefits, they are an excellent choice for drug delivery, as anticancer medications can be delivered to cells efficiently. Gene therapy has recently been considered in relation to siRNA-based gene silencing. This method improved the effectiveness of cancer treatment. Through the use of a disulfide linker, siRNA can be coupled to f-

CNTs, which can then cause the targeted cells to silence and die. [20] [22]



(Fig No. 10 Carbon Nanomaterial and their application in biomedical area [22])

Photoacoustic imaging (PAI) is a relatively new imaging method that has been widely applied in several biomedical domains. PAL produces ultrasonic emission, and an ultrasound microphone is capable of analysing all of these changes; these signals were then obtained and utilized to create 2D or 3D images . Compared to most optical imaging techniques, PAI's primary advantage is its ability to capture images of deeper tissues and provide higher spatial resolution. [23]

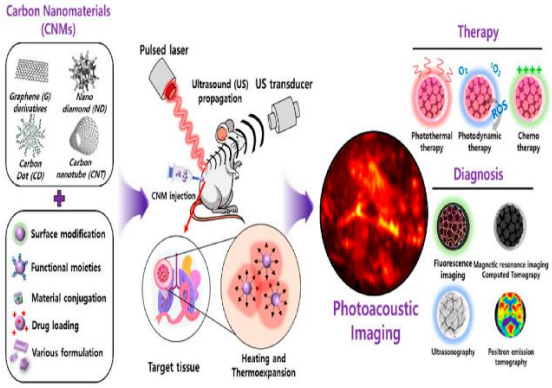


Fig No. 11 Illustration of carbon nanomaterial for photoacoustic imaging [24]

Studies have been done on CNT-based antitumor immune therapy. With this approach, tumor cell vaccines (TCV) were utilized, and inactivated cancer cells expressing tumor antigens stimulated the patient's immune system to fight the tumor itself . An amide bond can be formed between the oxidized MWCNTs and the proteins in the tumor lysate to covalently couple them in order to enhance the effectiveness of TCV. However, Villa et al. have been able to enhance the response to weak immunogenic peptides by using SWCNTs as antigen-presenting carriers [23]. Carbon nanotubes can also be used to treat cancer by raising its temperature. CNTs are useful biological imaging agents due to their fundamental optical properties, which include strong resonance Raman scattering as well as near infrared photoluminescence (NIR PL) in the 1.1-1.4 μm spectrum region . [25] Despite the numerous benefits of carbon nanotubes, their biomedical advancements have been restricted. CNT purification is currently in its early stages of development. However, the limited biomedical applicability of CNTs arises from their inability to dissolve readily in aqueous solutions; even though, this drawback can be addressed by functionalization. [20]

CONCLUSION

The field of cancer detection and therapy has been made significant progress in past few years. The

growing field of nanotechnology focuses on a variety of nanostructure designs which includes liposomes, carbon nanotubes, gold nanoparticles etc. that are coupled with an extensive spectrum of specialized targeting agents for clinical applications. The surface of the nanoparticles has the targeted agents attached to it, which facilitates the delivery and buildup of those agents within the cancerous tissue. The goal of nanotechnology is to substitute specific targeting agents with the potential to provide targeted delivery, controlled release of therapeutic cargo, assessment, visualization, and detection in place of highly invasive or nonspecific chemotherapeutic drugs.

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