RESEARCH ARTICLE

Potential Approaches of Nanotechnology for Cancer Therapy: An Insight

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ABSTRACT

Cancer is one of the most severe threats to people all over the world. Cancer incidence and mortality are also on the rise. Chemotherapy, surgery, and radiation therapy are examples of traditional cancer treatment methods. Chemotherapy has been widely used in clinics due to its simple and effective process; however, the therapeutic potential of cancer chemotherapy is severely unsatisfactory due to side effects and drug resistance, non-specific distribution of medicines, multidrug resistance (MDR), and cancer heterogeneity. A drug delivery system (DDS) that combines chemotherapy with supplementary cancer management is required to overcome these limitations and improve cancer therapeutic efficiency. Because of nanomaterials' distinct physicochemical and biological properties, nanotechnologies have presented high potential in cancer therapeutics in recent years. Nanocarriers such as nanodiamonds, quantum dots, high-density lipoprotein nanostructures, liposomes, polymer nanoparticles, dendrimers, nanoconjugates, and gold nanoparticles are used in drug delivery of their physicochemical and optical properties, adaptability, sub-cell size, and biocompatibility. They provide an efficient means of transporting small molecules and biomacromolecules to diseased cells/tissues. In context to cancer, it provides a unique approach and comprehensive technology for early diagnosis, prediction, prevention, personalized therapy, and medicine. As a result, combinational therapy based on chemotherapy facilitated by nanotechnology is the current trend in clinical research, resulting in significantly improved therapeutic efficiency with minimal side effects to normal tissues. The review focuses on recent developments and approaches in nanotechnology for cancer treatment.

Keywords: Cancer, Drug delivery, Nanocarriers, Nanoparticles, Nanotechnology.

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INTRODUCTION

Cancer is one of the leading causes of mortality worldwide. The pace of cancer is increasing with time because of factors like higher pollution, radiation, lack of exercise, and a balanced diet, including genetics.[1] Cancer control has been quite complex due to the distinctive pathophysiology of the cancer cells, which show therapeutic resistance and clinical diversity on the phenotypical and genetic levels. Any of these factors can lead to a mutation in cell DNA, including oncogenes, and causes cancer.[2]

The immortalization and longevity of discrete and amazingly replicated cells exceed all healthy functional cells and causes death ultimately. Initially, cancers start to spread to remote places throughout the body but are likely limited to a small area,[3] making cancer incurable. While our understanding of cancer biology has improved dramatically in the last 20 years, cancer is still the second leading cause of death in the world. More than 10 million new cases and more than 5 million illness-related deaths are reported every year.[4] A cancer analysis was considered earlier terminal, although the prognosis is favorable at an early stage. A considerable number of cancer patients are asymptomatic until the final stages of the disease are reached. Chemotherapy, radiotherapy, and surgery are among the most common cancer treatments.[5]

Chemotherapy is widely used to inhibit the growth of fast-growing cancer cells by the systemic administration of cancer medicines to patients.[6] A high volume of distribution for low-molecular active ingredients leads to cytotoxicity from chemotherapy. The primary clearance from systemic circulation is another major limitation of chemotherapy. Small molecular chemicals are promptly excreted. They are washed away by macrophages from the body. They, therefore, persist for a short period in systemic circulation and cannot be interconnected with cancer cells, resulting in lower therapeutic

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effects. To achieve a therapeutic impact, a greater concentration is needed for this purpose.[7] A low chemical therapeutic index suggests that the concentrations required for effective action are usually high, leading to systemic dose-dependent side effects in general.

Another problem that reduces their biological membrane penetration potential is the poor aqueous solubility of anti-neoplastic agents. A P-gp macromolecule of MDR is over-expressed, acting as an efflux pump and inhibiting the accumulation of the drug into the tumors on cancer cell surfaces.[8] This leads to drug resistance and eventually to chemotherapy failure.

The high sensitivity to degradation, mostly at the reticuloendothelial system (RES), allows the use of oral medication to be bypassed. Thus, the change can be well achieved through optimization of DDS in the management of available chemotherapeutics. The low solubility of drug may cause blood vessel embolization after i.v. injection, as insoluble drug accumulation leads to local toxicity due to high drug concentrations at the deposition site.[9] At present, thermodynamically stable polymer micelles consisting of a lyophilic center surrounded by a hydrophilic shell are investigated and identified as an efficient medicine delivery system.[10] In addition, the effectiveness of the drug is also limited if cancer cells have non-inheritable MDR. The typical feature of MDR is that the cell membrane P-gp, which can treat away from cells, is over-expressed. Many ways to keep the anti-neoplastic agent encapsulated in nanoparticles and co-administering P-gp-inhibitors away from P-gp-mediated MDR are expanded.[11]

Cancer cells may be damaged with radiation therapy. Due to the lack of treatments and clinical methods to prevent safe multidrug malignant growth, new progress has shown that further advancements are made in identifying and treating this disease right early because of inadequate treatments and clinical procedures to overcome MDR cancer.[12,13]

In this respect, numerous therapeutic ligand-based strategies are established to tackle problems identified with standard therapies and provide additional means for cancer clinical support such as immunotoxins, radioimmunotherapists, and drug immunoconjugate. Increased therapeutic efficiency with low to minimal side effects should lead to the destruction of cancer cells and the restriction of destruction on normal cells. There is a consequent need to develop new and creative advances in disease therapy that would encourage tumor margins to be outlined, residual tumor cells and micrometastases to be established, and the total removal of a tumor.[14,15]

Nanotechnology-based Promising Therapeutic Tools

Recent progress suggests that nanotechnology can profoundly affect the intervention of diseases, analysis, and treatments, which includes the fabrication of nanomaterials that show new properties.[16,17] The pattern and development of a nano-scalable device to upgrade its physical, compounds, and natural properties can be characterized by nanotechnology.[18]

Nanomedicine has incredible potential for revolutionizing the use of cancer and medicine through the development of ingenious biocompatible nanocarriers for drug delivery[17] (Figure 1). Nanoparticles (NPs) are biocompatible and biologically degradable and emerge from a center, a particle acting as a carrier, and a functional core group that focuses on specific locations.[15,16] The primary benefits of NPs are improved delivery of an imaging system and a drug, delivery of water-insoluble drugs, and targeted drug delivery. Since nanomaterials provide specific chemical and biological properties, the power of drug-targeted medical aid has increased significantly.

Nanotechnology-based cancer treatment is focused on various nanocarriers.[17,18] These nanosystems have four distinct characteristics, which can be recognized from other cancer therapeutics: (i) nanosystems themselves will have therapeutic or diagnostic properties, (ii) multivalent targeted ligands can be connected with nanosystems, which produce high affinity and specificity for target cells, (iii) multiple molecules of drugs that alter combinatorial cancer treatments at the same time can be developed to accommodate nanosystems, and (iv) nanosystems can circumvent old mechanisms of drug resistance. The intracellular concentration of cancer cells in therapeutic agents increased with the use of both passive and active targeting means while reducing the toxicity of the regular cells, simultaneously upgrading malignant effects and lessening systemic toxicity.[15-18]

Liposomes, polymeric NPs, dendrimers, nano-shells, inorganic, nucleic acid-based, and magnetic NPs are the most recognized nanocarriers for chemotherapeutic delivery.[19] Nanoparticular systems offer important advantages to cancer treatment over free drug use since NPs improve the therapeutic index of loaded chemical agents in comparison to typical doses, increase the efficacy of drug therapies through the achievement of steady-state drug therapeutic levels over a longer period, reduce pharmaceutical toxicity due to controlled

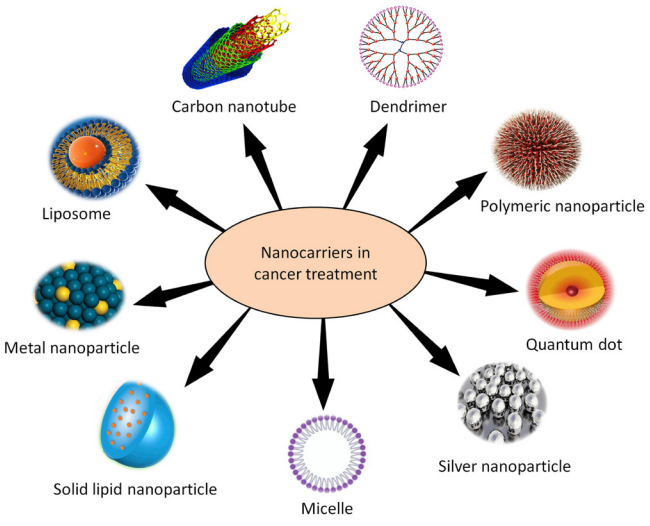

Figure 1: Schematic presentation of different nanocarriers used for cancer treatment

drug releases and improve pharmacokinetics by increasing drug solubility, stability and minimizing systemic clearance. It provides an opportunity to combine therapy with chemical and photothermal effects or facilitate the delivery of magnetic nanostructures by applying an external magnetic field.[20]

Therapeutic Nanomaterials in Treatment of Cancer

Nanomaterials are able to improve the specific distribution of macromolecular substances in the tumor tissue, improving medication suitability and reducing side effects by increasing penetration and maintenance.

Liposomes

Liposomes are round vesicles made of macromolecule bilayers that can spread through cell layers only to convey hydrophilic and hydrophobic substances to cells[19]. Liposomes are unilamellar or multi-lamellar circular vesicles made up of phospholipids. Liposomal formulations of many chemotherapeutic agents with promising results are currently in the pre-clinical and clinical field (Table 1).[20-22]

Nanoparticles

Nanoparticles are a group of particles that can be noted as focussing on ligands that are adaptable to chemical markers inserted in cells of malignancy to bind them. These ligands include aptamers, antibodies, different peptides, and cytokines. The NPs are colloidal nano-sized particles with a particular agent within or adsorbed or formed onto the surface of their polymer lattice. The NPs are focused on explicit sites through surface modifications, resulting in specific biochemical partnerships with the receptors on target cells.

Polymeric NPs that depend on engineered polymers or common polymers are highly bio-compatible with high drug loadings.[23] Many practical surface settings of polymeric NPs can also be modified to actively target certain antibodies, peptides, and other ligands. The PEG-changed on the outside of polymer nanoparticles protects them against blood clearance through the mononuclear phagocytic framework (MPS). Polymer-medicinal nanoforms are based on polymers while having novel characteristics. As its name implies, polymer-drug nanoforms are formations that bind polymer to bioactive covalently, increasing the blood circulation time, which permits anti-cancer bioactive to collect at the tumor.[24-28]

Dendrimers

Dendrimers are polymer-like nanocarriers with structures like stars or branches that can enhance malignant treatments' outcomes with the combination of therapeutic and/or diagnostic agents on the surface. Dendrimers are macromolecular compounds that comprise a series of branches around an inner core, thus functioning as an attractive way to deliver drugs.[27,28]

Table 1: Liposome-based cancer therapy[20-22]

Nanomaterials	*Drug*	*Used in the management of*
Liposomes	Daunorubicin	Kaposi's sarcoma
Liposomes	Cytarabine	Neoplastic meningitis
Liposomes	Doxorubicin	Kaposi's sarcoma, Ovarian, and breast cancer
Liposomes	Vincristine	Acute lymphoid leukemia
Liposomes	Mifamuride	Osteosarcoma
Liposomes	Irinotecan	Pancreatic cancer

Nanodiamond

Nanodiamonds are microscopic carbon-based agents that require high biocompatibility with other biologically diverse nanoparticles. The study was carried out by doxorubicin, which was used to transmit it into metastatic tumor cells or as biomarkers and tracers for cancer labelling.[29-31]

Carbon nanotubes

Carbon nanotubes (CNTs) belong to the fullerenes family. The CNTs show remarkable mechanical strength, high thermal and electronic conductivity. The smaller structure and mass of the CNT render it suitable as drug delivery and targeting vehicle. The CNTs are of different types, such as single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), triple-walled carbon nanotubes (TWCNTs), and multiple-walled carbon nanotubes (MWCNTs) (Figure 2).

The CNTs are used in biology as sensors for DNA and protein identification, screening devices for discriminating different serum sample proteins, and carriers for drugs, vaccines, or protein delivery. The CNTs may penetrate cells using a 'needle-like penetration' technique and deliver drugs in cytoplasm. The CNT can be functionalized by targeting molecules, antibodies, fluorescence molecules, and other multifunctional drugs.[30,31]

Polymeric micelles

A micelle is known as a group of amphiphilic surfactant molecules, and it is a key element of future cancer therapy. The first polymer micelle formulation is paclitaxel (PTX) formulated with cremophor EL, genexol-PM(PEG-poly (D, L-lactide)-PTX).[32]

Nanocantilever

A key tool for cancer detection, gene testing, and drug exploration is currently the micro-array approach for identifying complex biomolecular associations. Small bars

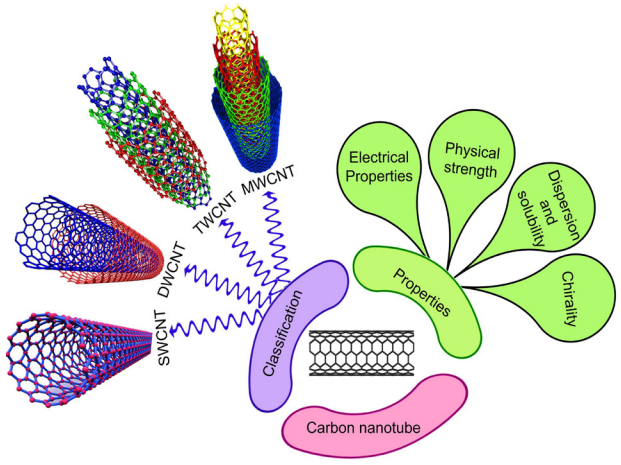

Figure 2. Classification and properties of carbon nanotubes

at one end are also intended to bind molecules associated with cancer. These molecules may bind to the proteins of modified DNA found in certain types of cancer. When bio-specific interactions develop between the receptor on one side of the cantilever and the solution ligand, the cantilever bends. When detected optically, the molecules of cancer can be identified, and therefore early molecular events in cancer growth are observed; when detection procedures occur, the ligand bends.[33,34]

Quantum Dots

Because of its scientific and technical importance in microelectronics, optoelectronics, and cellular imaging, the semiconductor quantum dots (QDs) received attention from many analytical teams. Semiconductor QDs are changing into a new class of biological and medicinal fluorescent labels. The wide absorption and small emission characteristics of QDs make it possible to use a single excitation source to make multicolor images. High quantum fluorescence, photobleaching resistance, and distinctive physical, chemical, and optical properties of QDs enable them to provide attractive candidates for *in vivo* molecular and cell imaging fluorescence tags for detection of cancer cells.[35]

Nanotechnology Mediated Advanced Cancer Therapies

Currently, cancer treatments are confined to surgery, radiation, and chemotherapy. All three approaches risk normal tissue damage or improper cancer eradication. Nanotechnology provides a mechanism to specifically and exclusively target cancer cells and neoplasms and improve the clinical efficacy of conventional radiation-based and complementary approaches to treatment. All of these result in reduced risk and an increased likelihood of recovery for the patient. The study of nanotechnological cancer therapy extends to develop novel therapeutics using nanomaterial properties.[35-37]

In comparison with cells, NPs are small enough to encapsulate a range of small, multi-category molecules. Similarly, the relatively wide NPs surface area is also compatible with ligands as well as small molecules, DNA, RNA, peptides, aptamers, and antibodies. These ligands are usually used to treat or to directly affect NPs *in vivo*.[38-40] These features allow combined drug supply, multi-modality therapy, and an integrated therapeutic and diagnostic approach called "theranostics". Physical properties of NPs, such as energy absorption and re-radiation, laser ablation, and hyperthermia can also be used to damage diseased tissues.[40-42]

A more desirable treatment for cancer has been targeted chemotherapy – where only cancer cells have been destroyed. New materials and methods for targeted cancer treatment have been developed (Figure 3). Designed NPs open up new non-invasive treatment techniques, including photodynamic therapy (PDT), photothermal therapy (PTT), radiotherapy, radiofrequency therapy, immunotherapy, and gene therapy.[43-47]

Photodynamic Therapy

Photodynamic therapy (PDT) is based on external electro-magnetic radiation. The efficient surface tumor treatment

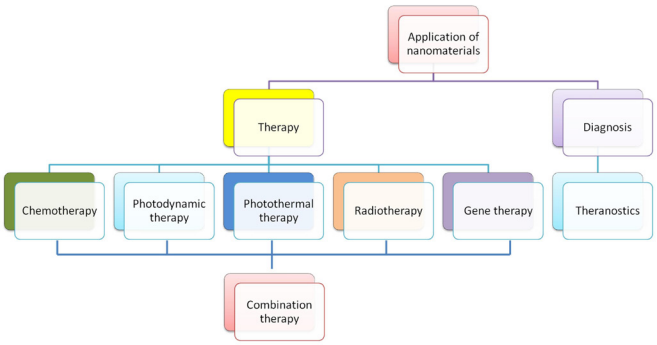

Figure 3: Application of nanomaterials in advanced cancer therapies

procedure depends on the photosensitizer position and light activation for cytotoxic reactive oxygen species (ROS). Typically made from high Z core lanthanide or haphnium doped, X-rays may be irradiated until absorbed, allowing visible light to be emitted from the tumor site by the NP core. The photon particle emissions to generate singlet following activation of a nanoparticle-bound or local photosensitizer.[48-51]

Photothermal Therapy Combined With Photodynamic Therapy

Due to low energy absorption and an insufficient penetration into biological tissues by near-infrared (NIR) PDT photosensitizers, extensive attempts have been taken to integrate PDT and PTT in a more effective therapeutic environment with a malignant tumor. The AlPcS4 photosensitizer complex gold nanorod (GNR) was developed by combining photosensitizer with gold nanoparticles (AuNPs). The results showed that tumor growth decreased by 79% only with PDT and 95% with the combination of PTT and PDT. These distinguished materials can absorb a wide range of wavelengths ranging from 500 to 1000 nm, both visible and NIR, generating substantial ROS and simultaneously combining PDT and PTT heat. In comparison to individual therapy, PDT and PTT combination has an improved synergistic effect of necrobiosis.[52-55]

Chemotherapy Combined with Photothermal Therapy

Chemotherapy and PTT combination have great potential in tumor treatment due to synergistic working. Multifunctional nanocarriers loaded with drug and photosensitizers have been developed for the purpose of synergistic therapy using direct therapeutic agents with photothermal material.[56]

Gene Therapy

The idea of introducing certain exogenous genes into the genome of the tumor cell for a tumor-causing effect is the basis of gene therapy. Improved therapies for nucleic acids, which are highly unstable in systemic circulation and vulnerable to degradation, are becoming apparent. This includes genetic engineering based on DNA and RNA, such as small interfering RNAs (siRNAs) and microRNAs (miRNAs) interference. The therapeutic silencing genes, i.e., siRNAs, transmitted either enclosed or conjugated to a NP, have significantly extended half-lives. These drugs are used for booting "unscattered" cancer proteins. Moreover, nanocarriers mediated increased

stability and controlled release of genes under genetic therapy have proved their effects.[57-59]

Nanotechnology-based Radiotherapy and Radiofrequency Therapy

There has long been a concern for the increase in the radiation dose. Various substances have been registered to cause more photoelectric absorbance in the tumor than in the surrounding tissues. It improves the radiation dose given to the tumor. A radiosensitizer and/or dose enhancer should significantly improve the therapeutic ratio in clinical terms and should be widely available, practical, and nontoxic[60].

Nanotechnology-based Cancer Theranostics

A new medicinal approach known as theranostics is the combination of imaging and therapy in a single step. The main aim of therapy is specifically for certain diagnostic and therapeutic accuracy of diseased tissues or cells. The combination of major phases of health care services, like diagnosis and therapy, with the help of nanotechnology, makes the treatment shorter, safer, and more reliable. The NPs have been used as carriers of diagnostic agents and drugs for several therapeutic approaches. Currently, biocompatible NPs are developed to enable non-invasive identification and accurate cancer therapy. Such NP-mediated combination strategies promise to boost therapy, reduce treatment side-effects and increase cancer cure rates.[60,61]

Radiofrequency Ablation

A radiofrequency ablation is an established approach for the destruction of the tumor. Nanotechnology makes it easier to generate non-invasive tumor cell radiofrequency destruction. The AuNPs *in vivo* and *in vitro* have been developed to support the non-invasive destruction of cancer cells. In addition to AuNPs, a new, non-invasive radio wave machine has been used to improve the thermal dissolution of tissue and cell cancer *in vitro* as well as *in vivo* systems.[62].

Nanotechnology-based Treatments in Combination with Chemotherapy

Various combination therapies, including chemo-chemotherapy combination treatment, chemo-radiation combination therapy, chemo-gene combination therapy, chemical-photothermal combinations, and chemo-thermodynamic combination therapy, have been investigated for the treatment of cancer.[20]

Chemo-chemotherapy Combination with Nanocarriers Based Therapy

Research suggests that MDR impedes the therapeutic results of traditional chemotherapy. The MDRs are complex because of several mechanisms for cell resistance, including enhanced efflux pump function, drug-induced repair of damaged DNA material, apoptotic pathways, and activation of detoxifying proteins. NPs based chemotherapy and MDR inhibitors are being developed in various studies to reverse MDR. For example, P-gp is one of the factors in MDRs that can reduce anti-cancer drug potential by quickly pumping drugs out of cancer cells because of reduced intracellular drug concentration.[61-63]

Chemo-radiation Combination Therapy

The most common therapeutic approach used to eradicate cancer cells is radiation-induced DNA interference and cell death. The efficacy of radiotherapy is, however, insufficient due to its toxic side effects. The simple combined approach with chemotherapy and radiation therapy often deliberately increases the toxicity. To resolve this constraint, chemotherapy and local radiotherapy are combined with the synergistic focus of biocompatible or biodegradable nano-platforms, which can achieve low radiation dose and low toxicity.[62,63]

Chemo-gene Combination Therapy

Genetic diversity and chemotherapeutics have been developed to treat cancer through precise control of the complex gene expression, like miRNA, siRNA, and short hairpin RNA interference. Since several genetic variants contribute to tumorigenesis, genetic heterogeneity leads to MDR. The Du-miRNAs are small RNAs that do not encode and influence the mRNA translation and diverse biological processes as miRNA targets several mRNAs. Thus, the miRNA technique can improve the results of cancer treatment through complex signaling pathways and proteins related to cancer.[60,63]

Chemo-photodynamic Combination Therapy

Photodynamic treatment involves a non-invasive, light-sourced, photosensitizing (PS) agent and oxygen treatment for cancer. Chlorines, porphyrins, and phthalocyanines are specified PS for cancer PDT. The PS is delivered into tumor sites and activated at a certain wavelength by a light source that creates ROS ($1O_2$, H_2O_2, O_2*, HO*). Like chemical therapies, PS can also be loaded into organic (e.g., liposomes, polymeric NPs, hydrogel) and inorganic nanocarriers (e.g., QDs, ceramic-based NPs, carbon materials, metallic NPs).[61-63]

Chemo-photothermal Combination Therapy

Chemo-photothermal combination treatment poses an interesting problem in various combined treatments depending on nanotechnology with ongoing times at a very basic level due to its safe and non-invasive photothermal treatment. The PTT turns light energy into thermal energy to increase tumor-site temperature and eliminate tumors and enhances the chemotherapeutic effects. The increased temperature improves the penetrability of the cell wall, allowing NPs to be more effectively collected in disease cells. Hyperthermia can reduce the expression of MDR-related genes, in this manner diminishing or conquering MDR malignancy cells, Further, hyperthermia can hinder the maintenance of damaged DNA produced by anti-cancer drugs, elevating the impacts of chemotherapeutic agents.[60]

Theranostic Nanoparticles based on Combination Therapy and Multimodal Imaging

The use of imaging methods in recognizing and managing malignant growth can reflect disease states and the biodistribution of therapeutic agents. Computed tomography (CT), positron emission computed tomography (PET/CT), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), ultrasound imaging (USI),

photoacoustic imaging (PA), and fluorescence imaging are examples of common imaging modalities. Specific agents are used in various imaging methodologies to increase imaging contrast. Contrast agents with high electron density and nuclear numbers, such as AuNPs, barium, and iodine compounds, are widely used as CT contrast agents. Nanoparticles labeled ^{18}F, ^{124}I, and ^{64}Cu, or ^{125}I and ^{125}Cd, can be used as PET or SPECT contrast agents to improve image contrast. Furthermore, in MRI, paramagnetic agents (e.g., Gd^{3+}, Mn^{2+}, or Fe^{3+}-based agents) and SPIONs improve T1 and T2 differentiation independently[60-63].

CONCLUSION

The use of nanotechnology in cancer therapy in recent years has been promoted exponentially. Various types of nanocarriers have enhanced the solubility of drugs and reduced toxicity towards the healthy tissue to overcome the constraints of standard chemotherapy. As the development of multifunctional nanocarriers is progressing, the drugs stacked in nanocarriers are explicitly directed at the site via passive and active targeting. Reasonably designed nanocarriers can avoid renal clearance that allows a prolonged period of circulation. The use of nanocarriers has improved the efficacy of an anti-neoplastic drug, but new challenges have arisen. Nanoparticles provide planning and tuning opportunities that are not feasible with other kinds of remedies. The multidisciplinary field of innovation is warranted to develop a safe and effective drug delivery system for the treatment of cancer.

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