Int. J. Nano Dimens., 12 (4): 310-327, Autumn 2021

REVIEW PAPER

Cancer nanomedicine: A review on approaches and applications towards targeted drug delivery

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Received 18 February 2021; revised 15 March 2021; accepted 07 April 2021; available online 10 April 2021

Abstract

Cancer prevails to be one of the main reasons of death across the globe. A large group of drugs and other therapies exist in the market for cancer treatment, yet, these conventional therapies have huge drawbacks such as low-specificity, off-target toxicity, and multidrug resistance that impact the standard of living of the patients. The concept of nanomedicine for targeted cancer therapy was able to overcome these problems, enhance the antitumor activity, and reduce systemic toxicity. Nanomedicine aims at utilizing properties of materials in the range of 1 to 100 nm for the treatment of diseases. Nanomedicine can achieve targeted therapy owing to the uncommon properties of nanoparticles and cancer itself. Cancer nanomedicine is used not only for treatment but its potential can also be expanded for early cancer diagnosis and tumor imaging. Many nanomedicines are currently in various phases of clinical trials and a few have already been authorized by the Food and Drug Administration for clinical use. This review highlights different approaches to targeted delivery of drugs and summarizes the utilization of various nanoparticles in targeted drug delivery, combination therapy, diagnosis, and imaging. Finally, this review also discusses the challenges that need to be overcome and provides an insight into future perspectives in the area of cancer nanomedicine.

Keywords: *Antitumor Activity; Cancer;Drug Delivery; Nanomedicine; Targeted Therapy.*

How to cite this article

Shameera Begum B.A., Faridha Begum I., Hemalatha S. Cancer nanomedicine: A review on approaches and applications towards targeted drug delivery. Int. J. Nano Dimens., 2021; 12(4): 310-327.

INTRODUCTION

Cancer is a primary public health concern and currently the second main reason for death worldwide [1-3]. It is the uncontrolled growth of cells with an indefinite capacity to undergo cell proliferation and is resistant to cell death [4-6]. The present therapy for treating cancer consists of surgery, chemotherapy, and radiation therapy but these conventional methods as standalone therapy possess several drawbacks [7]. The limitations of conventional therapies are the non-specific distribution of the drug, chances of developing multidrug resistance (MDR) [8, 9], rapid clearance of the drug, and poor targeting, all of which damages the normal tissues and causing side effects [10].

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Over the decade, advancements in various branches of science and technology resulted in the development of different methods for detection and treatment of cancer at an early phase and also to overcome limitations of conventional therapies (11). Nanomedicine utilizes all the aspects of nanomaterials for the diagnosis and treatment of diseases [12-15]. The size of the nanomaterials ranges from 1 to 100 nm [16]. The characteristics of nanomaterials are high surface-to-volume ratio; optical[17-19], electronic, biological[20-23], and magnetic properties that can be adjusted and they can be designed in different sizes[24-26], shapes[27], compositions[28], and surface modifications[29]. These properties of the nanomaterials can be incorporated in cancer therapy, drug carriers, combination therapy, and

diagnostics [12].

The use of conventional therapy is limited by its poor specificity which leads to off-target toxicities. The application of nanomedicine was successfully able to overcome this obstacle by offering target-based therapy. Targeted therapy aims at inhibiting certain pathways or molecules that have a crucial role in tumor growth and its advancement that are over-expressed in tumors to achieve cell death and avoid side effects [4]. The targeted therapy approach can be passive, active, or stimulus-responsive targeting of tumor tissues and cells. The use of nanomaterials for targeted drug delivery offers advantages like protecting the drug from degradation before reaching the target, increasing the rate of drug absorption into cancerous cells, enable better distribution and controlled timing of drugs to the tumors, and limiting the interaction of drugs with healthy tissues to avoid any possible side effects [16].

A total of 50 nanomedicines have been approved by the FDA until recently and over 100 products based on nanomaterials are in clinical trials. Hensify®, Vyxeos®, Onivyde®, Abraxane®, Doxil® are some of the FDA approved nanomedicines used for treating various types of cancers [30]. 18 new nanoparticles have entered clinical trials since 2016 out of which, 17 nanoparticles are designated for cancer [31]. This review focuses on different targeted drug delivery approaches current use of different varieties of nanoparticles in targeted delivery of drugs, applying nanoparticles in RNA interference (RNAi) therapy, combination therapy, cancer diagnosis, and imaging, the challenges associated with cancer nanomedicine that slows down its progress.

TARGETED DRUG DELIVERY APPROACHES

Passive targeting:

Passive targeting utilizes the uncommon aspect of the Tumor Microenvironment (TME) of the tumor mass known as the EPR or Enhanced Permeability, and Retention effect. The feature of the EPR effect is that molecules of a particular size preferably in the range of 100 - 1000 nm [32] can accumulate well in cancerous cells and tissues rather than healthy tissues. This is because the actively proliferating cancerous cells are in need of extra nutrients than the healthy tissues resulting in angiogenesis where new leaky blood vessels are formed **(Fig.1)**. These new, abnormal blood vessels develop increased vascular permeability aiding in the transport of molecules to the tumor tissues. This enhanced permeability varies according to the tumor type and the tumor's location [33]. Also, unlike normal tissues, the lymphatic drainage system in tumor tissues is defective which leads to increase accumulation and retention of the molecule in the tumor tissues.

The TME is crucial in the advancement of cancer and its metastasis to distant sites, hence it makes a good target that can be used to provide therapy to solid tumors [34]. Doxil™, Abraxane™, DaunoXome™, Myocet™, Genexol-PM™ are some of the passively targeted nano-formulations that are in clinical use at present. These formulations exhibit a considerable response rate when compared to the drug in its standard form [35]. The results are quite promising which could lead to progress in the field of cancer nanomedicine.

The EPR effect greatly depends upon the intrinsic tumor biology like the extent of the new blood vessel formation, the pressure within the tumor mass, and the advancement of the tumor itself along with the physio-chemical properties of the nanoparticle that is used in drug delivery [36]. The size, shape, surface properties, and charge of the nanoparticles influence the distribution and accumulation of the drug or active compound in the tumor tissues. The size of the nanoparticles should be larger than 4 nm and less than 200 nm for effective extravasation into the tumor tissue [37].

One of the main concerns in passive targeted delivery is that the nanoparticles are quickly cleared by the reticuloendothelial system (RES) which affects the effectiveness of the therapeutics as well as its safety profile [38]. To overcome this issue, nanoparticles coated with polymers like PEG were used. These polymer-coated nanoparticles displayed significantly increased half-life in blood circulation and lower clearance rates [12],for example, Paclitaxel albumin-bound nanoparticle (Abraxane™) [39].Another approach to reducing the clearance of nanoparticles is to mask them with cell membranes [40]. RBC-membrane-coated nanoparticles exhibited greater half-life and blood retention compared to PEGylated nanoparticles [41].

Thus, nanoparticles can be modified to passively target the tumor tissues to increase their specificity and selectivity to only tumor tissues and sparing the healthy tissues and additionally decrease toxic side effects, which conventional

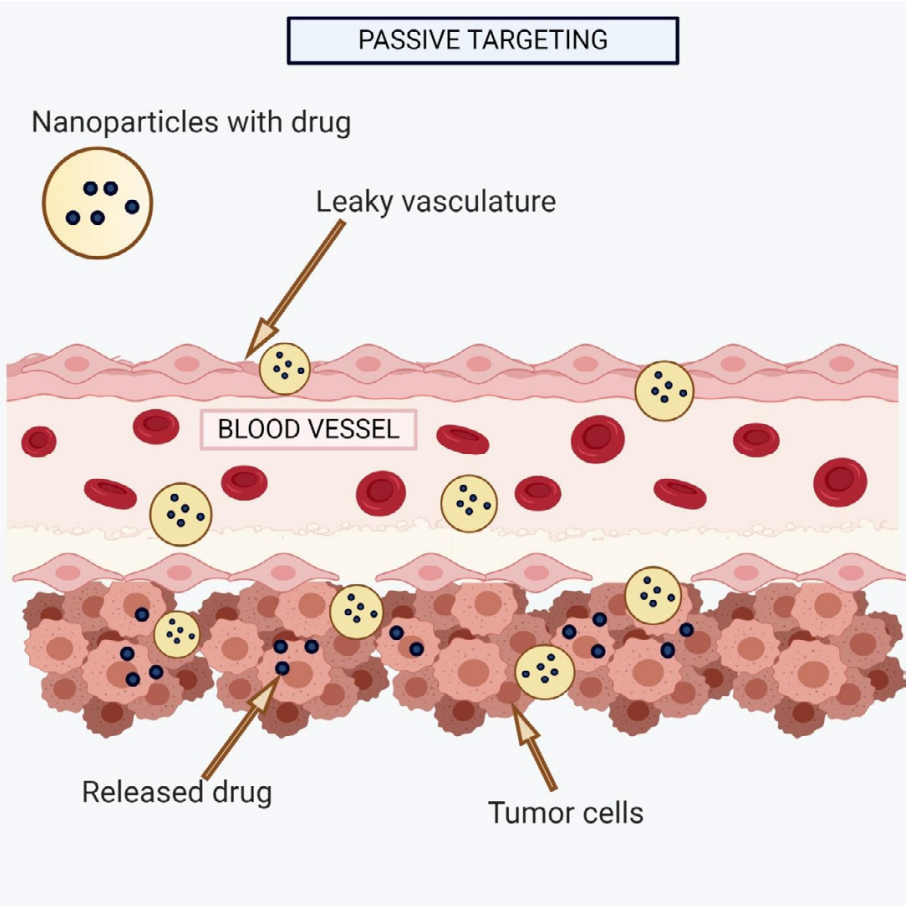

Fig. 1. Representation of passive targeting by Enhanced Permeability and Retention effect.

chemotherapeutic agents lack [16] making nanoparticles an attractive anticancer agent for effective targeted drug delivery.

Active Targeting

Active targeting also referred to as ligand-based targeting [42] depends on the interaction between the ligands that are conjugated or linked on the surface of the nanoparticles and receptors that are overexpressed on the malignant cells compared to normal tissues [43]. The nanoparticles or the drugs that are enclosed in a nanocarrier are internalized in the tumor tissues via Receptor-Mediated Endocytosis [44]. A variety of ligands and targeting receptors, have been identified and designed [45] to assist the progress of active targeting in targeted drug delivery approaches. Antibodies, peptides, vitamins, aptamers, and carbohydrates are some of the ligands used in active targeting [42]. Receptors such as Folate receptor (FR), Transferrin receptor [44], Estrogen receptor (ER), HER2/ Human Epidermal Growth Factor Receptor are targeted by the ligands. Immune cells such as Dendritic cells (DCs) are also targeted [46-51]**(Fig. 2)**.

In the active targeting approach, the nanoparticles are surface-functionalized in a way that they only interact with the cells that overexpress the particular receptors, thus increasing the precision and the effectiveness of the drug delivery system [33]. Active targeting of glycyrrhetinic acid receptor (GA-R) using surface-functionalized nanoparticles shows enhanced delivery of the drug to the lesion and relatively safer with reduced side effects [52]. Another research showed that targeting vitamin uptake receptors using biotin anchored dendrimer showed effective internalization in malignant cells along with increased cell inhibition and penetration when compared with the non-targeted delivery systems or free drugs [53].

Functionalization of the nanoparticles also

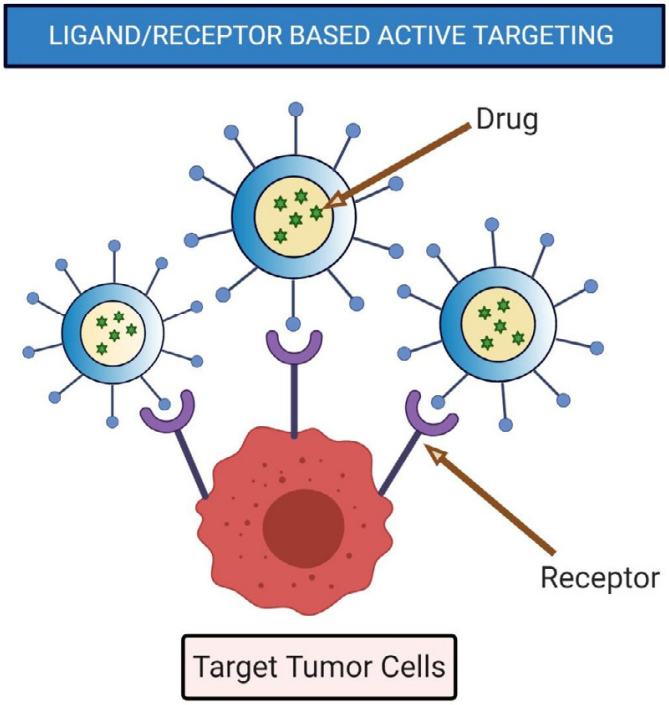

Fig. 2. Depiction of active targeting/ ligand-based targeting approach.

enhances their interaction with the tumor tissue and decreasing interaction with the healthy tissue [16]. One of the important features of breast cancer therapy using nanomedicine is to target biomarkers [54]. Delivery of tamoxifen using polymer nanoparticles targeted to Estrogen receptor (ER) in breast cancer cells showed very low cytotoxic activity towards the healthy tissues [46]. Functionalization of nanoparticles with monoclonal antibodies is also a promising strategy in targeting over-expressed antigens on cancer cells [45]. Sialyl -Lewis A (sLeA) is an antigen overexpressed in metastatic gastric cancer cells that is responsible for spreading cancer to distant sites [55]. Loading 5-fluorouracil and paclitaxel in sLeA targeting monoclonal antibody functionalized PLGA [poly(lactic-co-glycolic) acid] nanoparticles showed high affinity towards cancer cells expressing sLeA antigen and limited affinity for healthy tissues [56].

Peptides also make desirable ligands due to their low production cost, lack of difficulty in conjugation, and better stability. The arginylglycylaspartic acid (RGD) peptide is known for targeting over-expressed integrins in cancerous tissues [43]. Some of the nanoparticle formulations on ligand-receptor based targeting that entered research are SGT 53 (a cationic liposome formulation that targets transferrin receptor using anti transferrin scFv ligand), MBP-426 (a liposome formulation that targets transferrin receptor using transferrin ligand), and MM-302 (liposome formulation targeting HER2 receptor using anti-HER2 ligand) [33].

Active Targeting of nanomedicine displays considerable drug internalization, accumulation, as well as specificity to the targeted tumor cells than standard drugs or passive targeting systems [36] making them a superior targeted drug delivery approach.

Stimulus responsive targeting

The stimulus-responsive targeted drug delivery approach is drawing attention due to its reduced uptake by the healthy tissues while selectively targeting the tumor tissues [57]. They consist of nanoparticles with added components that can be activated by a particular stimulus for the controlled behavior of particles and enhanced targeted delivery [58]. This stimulus can either be external (light, magnetic field, ultrasound) or internal (pH, temperature, enzymes) depending on the nanoparticle preparation [45]. These stimuli-responsive nano-preparations exhibit

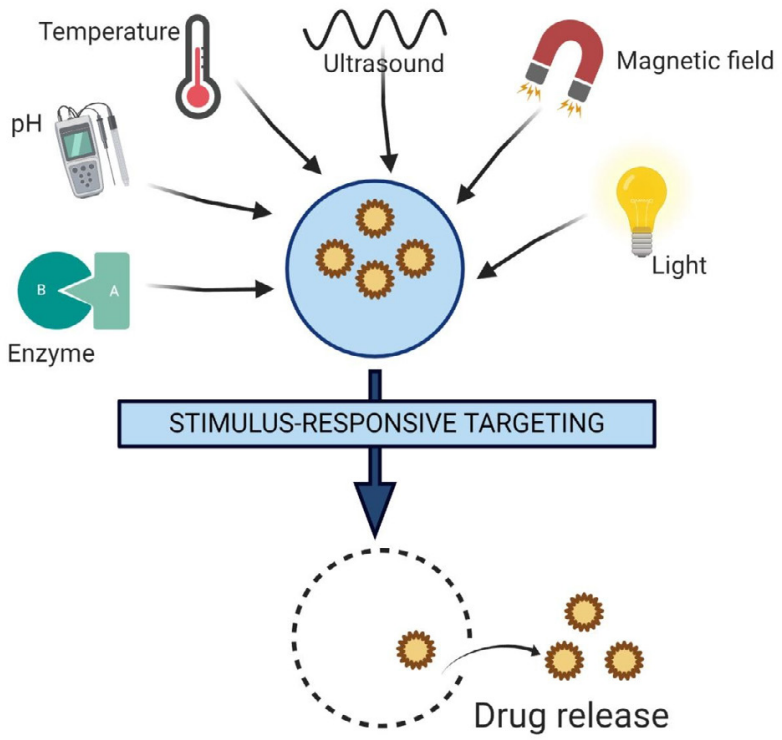

Fig. 3. Illustration of stimulus-responsive targeting promoted by external and internal stimuli.

better outcomes with regard to drug fate, drug release, and drug internalization by altering the nanoparticle's behavior [59] **(Fig.3)**.

pH-responsive approach

A significant aspect of the tumor microenvironment in solid tumors is their acidic pH, which leads to the development of invasive cancer cells and higher resistance to anticancer drugs [60]. This aspect of the solid tumor microenvironment can be used to design pH-sensitive nanoparticles [59]. An orally administered pH-triggered PAA [poly(acrylic acid)] capped mesoporous SBA-15 drug delivery system was developed which displayed a significant drug loading capacity of 785.7 mg/g, exceptional responsiveness to pH, also satisfying biocompatibility within colon cancer. Studies reveal its application in the delivery of the drug Doxorubicin (DOX) showed targeted release of drug in colon conditions having pH 7.6 [61].

Thermo-responsive approach

In certain diseases, local hyperthermia is observed. This observation led to the concept of thermo-sensitive nano-preparations in which an external heat supply is applied to stimulate the nano-particles [59]. Hyperthermia involves local heating of the tumor at a temperature range of 40 to 43ºC [62]. If the temperature is greater than 55 ºC, it is called High-temperature hyperthermia which is used in tumor ablation whereas Mild fever-range hyperthermia (40-43ºC) can be used to heighten the sensitivity of cancer cells to anticancer drugs, enhance drug delivery and trigger immune system against cancer cells [63]. Recently, Nanoparticle-mediated Photothermal therapy (PTT) is developing very quickly as a cancer therapy especially utilizing gold nanoparticles (AuNPs) because they have several advantages including tumor-specific heating [64]. Hyperthermia therapy is currently used in combination with chemotherapy as a promising cancer treatment [57]. A thermo-sensitive yolk-shell nano-particle with magnetic iron oxide nanoparticle core and thermo-responsive polymer poly (N-isopropylacrylamide) PNIPAM shell with a drug loading hollow space for DOX displayed excellent synergistic effect and an exceptional increase in tumor inhibition rate (40.3 % to 91.5%) upon irradiation [65].

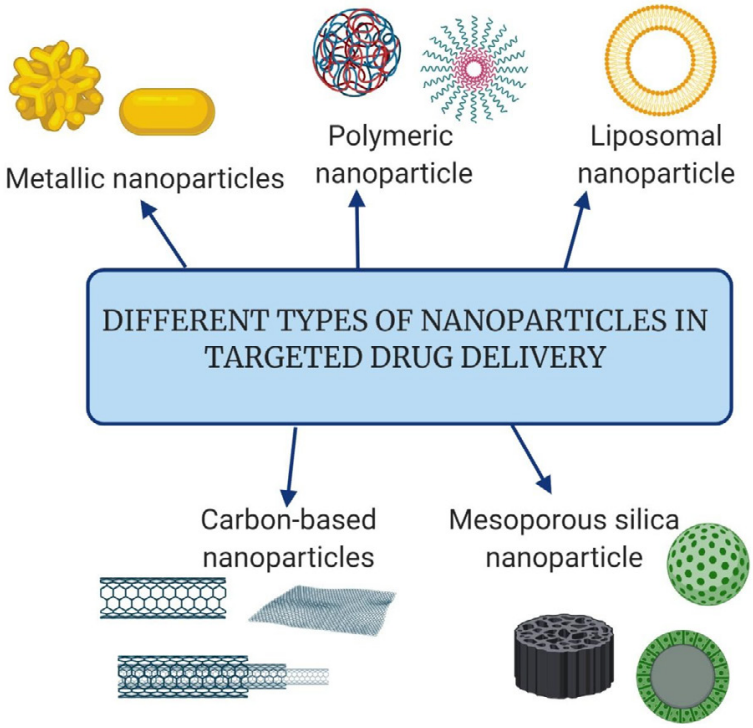

Fig. 4. Overview of nanoparticles identified for targeted drug delivery.

Enzyme-responsive approach

Enzymes play a vital role and are important in various biological processes. The presence or levels of different enzymes present or associated with different types of cancer can be exploited to design enzyme-responsive drug delivery systems [59]. Matrix metalloproteinases (MMPs), Cathepsin B, and Hyaluronidase are some of the enzymes connected with tumor-cell proliferation [57]. Methotrexate conjugated in glycine coated magnetic nanoparticles (F-Gly-MTX NPs), released methotrexate in the presence of proteinase K via peptide bond cleavage. The cytotoxic and enzymatic release studies indicate impressive anticancer effects of F-Gly-MTX NPs for breast cancer cell lines [66].

Light-responsive approach

Light-sensitive nano-preparations are a potential tool in cancer therapy which is achieved by altering certain parameters like wavelength, intensity, etc [59]. These systems are non-invasive and can be used for the “on-demand” release of drugs [57]. NIR light-responsive polymeric nanoparticle of copolymer inserted with selenium and loaded with the drug (I/D-Se-NPs) exhibited enhanced cell damage and generated continuous drug release upon irradiation. It further showed effective drug accumulation on the nucleus with no toxic side effects to the liver, kidney, spleen, lung, and heart [67].

Magnetic-responsive approach

Magnetic nanoparticles are able to break the biopolymer boundary to deliver the drug as well as trigger the release of drugs attached to these magnetic nanoparticles [59]. The nano-preparations are magnetized by different methods [59] and exposed to a magnetic field for tumor targeting applications [57]. Magnetic Mesoporous Silica Nanoparticles (MMSNs) exposed to altering the magnetic field displayed a synergistic effect and significant tumor growth inhibition [68].

NANOPARTICLES IN TARGETED DRUG DELIVERY

A large number of studies are being conducted to investigate the capabilities of nanoparticles for targeted drug delivery techniques in cancer nanomedicine although nanoparticles are not often used in clinical treatments [46]**(Fig.4)**. These nanoparticles can be broadly classified into metallic nanoparticles (47, 48), polymeric

nanoparticles, carbon-based nanoparticles, liposomal nanoparticles, mesoporous silica nanoparticles, quantum dots, dendrimers, etc.

Metallic nanoparticles

Metal nanoparticles have also been widely studied in targeted drug delivery systems for cancer therapy. They display several properties that can be exploited for use in nanomedicine and they can be prepared in different shapes and sizes as well as modified for selective targeting of tumor cells [70]. The size of the metal nanoparticles ranges from 1 to 100 nm [71, 72, 73]. Gold, silver, platinum, iron oxide, zinc oxide is some of the nanoparticles that are studied for targeted cancer therapy.

Gold nanoparticles possess unique characteristics and exhibit considerably low toxicity when used in targeted drug delivery systems [46, 47]. The combination of gold nanoparticles attached with programmed death-ligand 1 antibody (αPDL1) and computed tomography imaging enabled to non-invasively measure the number of nanoparticles accumulated in the tumors to predict the therapeutic outcome and the nanoparticles also prevented the growth of the tumor effectively with less amount of dosage [74]. In vitro findings of PEGylated gold nanoparticles enhanced the activity of varlitinib by effectively internalizing them in pancreatic cancer cells thus increasing the toxicity of varlitinib in MIA PaCa-2 tumor cells in comparison to the free drug [75].

Silver nanoparticles are extensively used in numerous fields in different forms such as nanorods, nanocubes, spherical nanoparticles, etc because of their special thermal, optical, and biological characteristics [76]. Silver nanoparticles are also highly specific with improved bioavailability compared to conventional agents [77, 78]. Evidence also shows that silver nanoparticles synthesized from natural extracts were involved in the induction of apoptosis in MCF-7 human breast cancer cell lines [79-80]. Silver nanoparticles biosynthesized from *Nepeta deflersiana* induced cell death in HeLa cells with an increase in the generation of reactive oxygen species (ROS) and LPO (lipid peroxidation) and reduction in mitochondrial membrane potential and glutathione levels, thus displaying anticancer potential [81]. Silver nanoparticles coated with albumin displayed significantly greater cytotoxicity in cancer cells than in normal cells and induced apoptotic cell death, also reducing the tumor size in mice. Furthermore, the LD_{50} value of silver nanoparticles against the breast cancer cell line (5μM) was 30 times greater than the LD_{50} value for normal white blood cells (152 μM) [82].

Among the drugs that are currently available for cancer treatment, platinum-based drugs are of importance, for example, cisplatin [83]. The results of conventional therapy for hepatocellular carcinoma (HCC) are not adequate because of chemo-resistance and recurrence. Novel pH-sensitive platinum nano-cluster assembly (Pt-NA) is able to induce DNA damage in HCC cells and in addition, down-regulates a myriad of genes that are important for tumor proliferation and also overcomes cisplatin resistance [84]. Platinum nanoparticles coated with peptide displayed higher cytotoxicity and cancerous cell selectivity in hepatic cancer cells compared to cisplatin and further, these platinum nanoparticles did not affect normal cells [85].

Iron nanoparticles are being explored for its use in diagnostics and as imaging agents for cancer therapy and have effective targetability and can be surface functionalized [86]. SPIONs or Super-paramagnetic Iron Oxide Nanoparticles especially gained increased recognition because they can be used in imaging as contrast agents and in chemotherapy due to its inherent magnetic properties and biocompatibility [46]. Functionalized SPIONs allow accurately tracking the nanoparticles inside the cells and also DOX release in the cancer cells of human pancreas. These nanoparticles can be detected using MRI [87]. SPIONs targeted to Epidermal Growth Factor Receptor (EGFR) exhibited increased confinement of SPIONs in the tumor and additional magnetic hyperthermia treatment led to tumor growth inhibition in lung cancer (NSCLC) orthotopic mouse model [88].

Zinc oxide nanoparticles exhibit selective toxicity against cancer cells and are promising agents for cancer therapy [89]. But only a few studies on human cancer cell lines have shown anticancer activity of zinc oxide nanoparticles [90]. Nanoparticles of zinc oxide, coated with lipids, displayed increased cell death because of the generation of reactive oxygen species that was due to effective internalization of nanoparticles in HeLa cells [91]. Biosynthesized zinc oxide nanoparticles induced apoptosis and specific cell cycle arrest in MCF-7 cancer cell line [92].

Polymeric nanoparticles

Polymer-based nanoparticles are colloidal particles produced by attaching a copolymer to another polymer matrix [46]. They are capable of altering drug activity and regulate drug release, hence have drawn attention in various fields of research [71]. The main characteristics of polymer-based nanoparticles are biocompatible, biodegradable, less toxic, increased circulation time [93], and a high solubility and drug loadability [46]. The anticancer drug is attached to the polymer either by adsorption, conjugation, or encapsulation and can be used for both active and passive targeting [93]. Polymer-lipid hybrid nanoparticles synthesized to release doxorubicin hydrochloride against multidrug-resistant breast cancer cells showed an 8-fold increase in the inhibition of tumor cells in comparison to free DOX solution in the same dose. These nanoparticles also increased the uptake and retention of the drug by the multidrug-resistant cancer cells [94]. For the production of polymer-based nanoparticles, natural polymers like chitosan, proteins, or synthetic polymers like polylactide, polyanhydride can also be used [52].

Chitosan offers low toxicity, biocompatibility, and structural versatility while serum albumin, another natural polymer, is non-toxic, non-immunogenic, and shows high specificity [52]. Novel pH-sensitive chitosan nanoparticles encapsulated with quercetin for delivery to breast cancer cells displayed applicable blood biocompatibility. The nanoparticles entrapped nearly 83% of quercetin while most nanoparticles concentrated on the surface and few were internalized [95]. Synthetic nanoparticles are widely used in drug delivery systems because of their high purity and controllable performance but when compared to natural polymers, they display poor compatibility [52]. PLGA nanoparticles employed for the co-delivery of rapamycin and piperine (chemo-sensitizer) exhibited improved absorption of rapamycin from the polymer nanoparticles in comparison to its counterpart and superior effectiveness of the nanoparticles than the free drug solution [96].

In an aqueous solution, amphiphilic block copolymers self-assemble resulting in the formation of spherical Polymeric micelles. These polymeric micelles can be used for passive targeting since they have extended circulation time, further can also be used for active targeting [97]. Simultaneously delivered cisplatin prodrug and paclitaxel combination using polymeric micelles demonstrated higher antitumor activity due to the equal delivery of both the drugs in cisplatin-resistant ovarian and breast cancer mouse models. The higher antitumor activity was found to be associated with the decreased drug release rate brought about by the polymeric micelle [98].

Carbon-based nanoparticles

Graphite, fullerenes, carbon nanotubes, nanodiamond, reduced graphene oxide, carbon dots are some of the carbon-based nanomaterials that are being employed for various purposes in a variety of fields [71]. They possess excellent biocompatibility, reduced toxicity, small size, thermal conductivity, optical and electrical properties [46]. Carbon-based nanomaterials have elicited much interest in biomedical fields [99].

Carbon nanoparticles/doxorubicin@SiO_2 for combined chemo-photothermal therapy significantly improved drug release upon light irradiation. These carbon-based nanoparticles also exhibited outstanding ability to generate heat [100]. Functionalized nanographene oxide (NGO) for chemo-photothermal therapy demonstrated that these functionalized NGO are perfect nano-carriers with more than 100% loading ratio for delivering DOX. Moreover, results revealed that they increased the efficiency of anticancer therapy and could distribute heat and drug to the specific tumor sites [101]. Currently, due to their photo-luminescence properties, carbon nanoparticles are gaining more importance. Functionalization of crystalline carbon nanoparticles with three different organic dyes at an excitation wavelength of 225 nm displays maximum fluorescence intensity while fluorescein functionalized nanoparticles showed the maximum fluorescence intensity. A minimal amount of cytotoxicity was observed when these nanoparticles were introduced into healthy human blood cells rich in erythrocyte [102].

The development of carbon nanotube has led to its application for various biomedical uses [103]. They are long, hollow, cylindrical structures composed of rolled graphene sheets. They are of two types, SWCNTs or single-walled carbon nanotubes and MWCNTs or multi-walled carbon nanotubes and they display great optical, electrical, and thermal properties [24]. Functionalized multi-walled carbon nanotubes conjugated with

paclitaxel (PTX) were able to release quickly at pH <7.4 which is perfect for release in the tumor environment. These functionalized MWCNTs also showed better penetration and cytotoxicity than free drugs [104].

Liposomal nanoparticles

Liposomal nanoparticles are vesicles of spherical shape produced by combining one or more phospholipid bilayers [46]. The vesicles can be of 0.025 µM (small vesicles) or 2.5 µM (large vesicles) based on their difference in size [105]. Phosphatidylethanolamine (PDE), phosphatidylcholine, cholesterol are some of the commonly used materials for creating liposomes [71].

Liposomes are one of the most popular and extensively investigated drug delivery systems [106]. The liposomal drug delivery system improves the pharmacokinetics and pharmacodynamics of many anticancer drugs and liposomes are also biocompatible, non-immunogenic, highly soluble, tumor-specific, and less toxic [107]. One main drawback of the conventional liposomes was their rapid clearance by the mononuclear phagocyte system (MPS) as a result of which many new formulations were developed to evade MPS clearance and increase stability and circulation time [106]. Many liposomal formulations are now attaining clinical approval due to their effective drug delivery to the target site and longer circulation period [105]. Liposomal amphotericin B (AmBisome®, Amphotec®), Stealth liposomal doxorubicin (Doxol®/ Caelyx™), Liposomal daunorubicine (DaunoXome®), Liposomal cytosine β- arabinoside (DepoCyt®) are some of the available liposomal drugs [108].

Mannosylated liposomes encapsulating two drugs (dihydroartemisinin and doxorubicin) resulted in a high amount of DOX accumulation in nuclei, thus maximum cytotoxicity since the mannosylated liposomes modified the intracellular distribution of the drug. Further, the mannosylated liposomes increased the tumor inhibition rate (88.59%) than free drugs in HCT8/ ADR tumor model [109]. Liposomes loaded with DOX and erlotinib exhibited good biocompatibility, increased accumulation of DOX and erlotinib, and enhanced antitumor activity with no toxicity [110].

Mesoporous silica nanoparticles

MSNs or Mesoporous silica nanoparticles have been recognized in targeted therapeutics because of their unique characteristics such as large surface area, ease of functionalization and surface modification, excellent biocompatibility, high drug loading capacity, the capability to adjust pore and particle size, and significantly low toxicity. Moreover, MSNs can be developed for targeting tumors passively or actively [111]. Functionalized mesoporous silica nanoparticles encapsulated with vorinostat (inhibitor of class I histone deacetylases) exhibited better solubility and permeability compared to free drugs. Further, the antitumor activity greatly improved in colon cancer cells and cutaneous t-cell lymphoma cells when using functionalized mesoporous silica nanoparticles than free drug [112]. Novel mesoporous silica nanoparticles-based nano-carriers attached with targeting peptide RGD and loaded with 5-fluorouracil effectively internalized in colon cancer cells and improved accumulation. 5-fluorouracil loaded mesoporous silica nanoparticles demonstrated enhanced antitumor activity with reduced side effects and tumor proliferation [113].

NANOPARTICLES IN RNA INTERFERENCE (RNAI) THERAPY

One of the major advancements in the field of cancer therapy over the last few decades is the advent of RNA interference (RNAi) therapy which reformed the approaches towards cancer treatment upon its emergence. This technique is used in the inhibition of the expression of those genes which are involved in inducing diseases, with the help of RNA molecules. This therapy employs different types of RNA molecules such as the siRNA, shRNA, and the miRNA to inhibit gene expression [114]. RNAi offers the advantage of higher target selectivity to many proteins and genes which are incapable of pharmacologically being targeted or in other terms “undruggable” owing to the absence of drug inhibitors, distinct drug-binding sites among other limiting factors [115]. Although RNAi therapy offers attractive treatment strategies, there are several hindrances involving the stability, delivery, specificity, and toxicity of the siRNA employed in the therapy [116]. Nanomaterials like organic and inorganic nanoparticles are able to provide several advantages over the conventional RNAi therapy because of their unique features which bring about improved stability, protection, transportation, and accumulation of siRNA thus

presenting itself as a promising non-viral delivery vehicle for RNAi therapy [117].

Cell division cycle 20 (CDC20) is an mRNA that functions as a proto-oncogene as well as interrelated with hypoxia in tumor tissues in breast cancer cells. In order to silence the expression of CDC20 oncogene, a Hypoxia-responsive nanoparticle (HRNP) of 2-nitroimidazole- modified polypeptide and cationic lipid were synthesized for specific targeting of the CDC20 oncogene which disassembles under hypoxia to discharge the contents. This HRNP displayed increased accumulation in tumor cells under hypoxia and exhibited adept silencing of CDC20 oncogene and in vivo suppression of tumor cells, thus being a promising approach in the treatment of breast cancer [118]. The use of hybrid nanovesicles of cationic polymer and lipid for the delivery of DOX and siRNA was effective and also found to activate the PARP 1 [poly (ADP- ribose) polymerase 1-dependent] apoptosis pathway leading to the cell death of B16 melanoma cells in mice through heightened expression and presentation of tumor antigens on site. This novel polymer- lipid nanovesicle could contribute to new treatment approaches for advanced tumors by facilitating a vast combination of anticancer drugs and RNAi therapies owing to its versatility and high stability [119]. The in vitro studies of chitosan-coated gold nanoparticles synthesized through layer by layer assembly revealed that these nanoparticles were able to excellently protect siRNA from degradation by enzymes, demonstrated better siRNA uptake and gene silencing in non-human small cell lung carcinoma cells than the commercially available lipofectamine and jetPET transfection reagents [120].

NANOMEDICINE-BASED COMBINATION THERAPY

Applying combination therapy in cancer treatment is an emerging approach. Combination cancer therapy is the simultaneous delivery of different anticancer drugs for the treatment of cancer and this offers advantages like reducing drug resistance, the synergistic effect, and increasing the potential of drugs [121]. However, administering more than one anticancer agent is quite challenging and has certain limitations [122]. The development in the field of nanotechnology and oncology has introduced several strategies to overcome the limitations in combination cancer therapy. Co-delivery of multiple anticancer agents encapsulated using nanocarriers is a promising approach and it is also more efficient than the conventional combination therapy [123]. Cell viability studies of co-delivered cisplatin and doxorubicin using polyamidoamine dendrimer reported high tumor growth inhibition on breast cancer cells as well as decreased the toxicity of doxorubicin [124, 125]. Another study demonstrated that co-delivering docetaxel and curcumin prodrug targeted to EGFR exhibited strong anti-tumor activity than non-targeted and monotherapy formulations for prostate cancer treatment [126].

Nucleic acids (DNA, RNA, and siRNA), monoclonal antibodies, or epigenetic drugs can also be used in combination with anticancer drugs using the co-delivery approach [50]. Some of the combination chemotherapeutic drugs approved by the FDA are,(1) Abraxane and Gemcitabine are for treating metastatic adenocarcinoma of pancreas, (2) Cisplatin, Paclitaxel, and Bevacizumab are for treating metastatic cervical cancer, (3) Ipilimumab and Nivolumab have been combinated for treating metastatic colorectal cancer and (4) Ribociclib and Aromatase are inhibitor for treating metastatic breast cancer [123].

Combining chemotherapy and siRNA for cancer treatment increases the efficiency of both drug and siRNA than using them alone because their co-delivery provides advantages like enhanced therapeutic effects, decreasing drug resistance, and lower side effects [126]. The application of Photo-thermal therapy (PTT) independently is not good enough since it can lead to tumor recurrence, however the combination approach of immunotherapy and PTT has the potential to minimize the recurrence and inhibit tumor metastases [64]. PTT therapy in murine melanoma model using gold nanoshells induces pro-inflammatory expression of cytokines and chemokines leading to dendritic cell maturation, thereby preparing antitumor T cell response [127]. Similarly, the combination of PTT and chemotherapy is also promising and has the potential to improve the effect of therapy and also reduce toxicity to healthy cells [64]. The combination of chemo- and photothermal therapy using silica nanoparticles for the co-delivery of Cetuximab (Cet) and indocyanine green (ICG) which is a photothermal agent, demonstrated greater anticancer activity compared to Cet or ICG alone for breast cancer treatment [128]. A

novel nano complex loaded with cisplatin and gold nanoparticles for chemo-photo-thermal therapy exhibited significant tumor growth inhibition, suppressing up to 95% of tumor growth and in addition, had the potential to remove microscopic residual tumor in colorectal tumor model [129].

NANOPARTICLES IN CANCER DIAGNOSIS AND IMAGING

Traditional methods of cancer diagnostics have certain limitations such as sensitivity and lack of specificity [130]. Nanoparticles have significantly enhanced diagnostics and therapeutics in different cancers because they possess several advantages like small size, biocompatibility, efficient drug loading capacity, enhanced specificity [131]. To identify the early-stage tumors accurately, nanomaterials have been designed which can treat tumors along with reducing toxicity [132]. The topically applied EGFR and HER2 targeted SERS (Surface-enhanced Raman scattering) nanoparticles on the surface of rat esophagus were able to visualize and locate the tumor precisely. Additionally, the quantification of EGFR and HER2 expression levels were in accord with the results from the flow cytometry [133].

Near-infrared fluorescence imaging (NIRF) is a promising detection technique for initial tumor stages because they display several advantages like high sensitivity, ease of conjugation, and synergistic effect for achieving diagnosis and treatment at the same time [134]. An actively NIR fluorescent probe with a near-infrared (NIR) dye and a quencher dye was developed for imaging Fibroblast activation probe- alpha (FAPα). FAPα is a cell surface protein that is expressed majorly in tumor tissues and is responsible for the growth and invasion of cancer cells. This NIRF probe was able to concentrate on tumors expressing FAPα exhibiting high specificity, exhibiting its capacity to detect early-stage cancer [135].

Optical Coherence Tomography (OCT), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT) are some of the current single imaging techniques used for the detection of cancer at different stages, however, they have certain limitations which can be reduced by the use of multi-imaging approach using multimodal nanoparticles [132]. Self-assembled glycol chitosan (GC) probe-based tumor targeting nanoparticles were prepared for optical/MR dual-modal imaging. The localization of nanoparticles within the tumor was favorable and the dual imaging by the combination of optical and MR provided high tumor tissue resolution and sensitivity [136]. Furthermore, nanoparticles are employed as contrast agents in a greater number for molecular Photoacoustic imaging (PAI) among which Gold nanoparticles are the suitable candidate for imaging due to their unique photophysical properties and several other characteristics [137].

The application of Fluorescent nanoparticles (FNPs) is also desired in cancer diagnosis because they offer several advantages such as high sensitivity, biocompatibility, strong signal strength, ability to tune, and strong signal strength [138]. Iron oxide nanoparticles along with fluorescent labels aids in the precise identification of tumor margin through fluorescence-image guidance [132]. Cyanine fluorescent dyes were used in the ablation and imaging of tumor cells because they were able to convert light into heat upon irradiation by NIR [131]. The cell membrane technology has been investigated to camouflage many different types of nanoparticles to overcome some of the limitations of regular nanoparticles-based targeted delivery [139]. Platelet coated Fe_3O_4 magnetic nanoparticles were synthesized which exhibited long blood circulation and cancer-targeting ability due to the presence of platelets. The results also demonstrated that these platelet-coated nanoparticles can be used to improve magnetic resonance imaging of tumor tissues for therapy and personalized diagnosis [140].

Currently, fusing Indocyanine green (ICG) into nano-platforms for application in cancer diagnosis and therapy has gained lots of interest because incorporation of ICG into nanoparticles significantly reduces its limitations like short half-life, non-specific targeting, etc [141]. ICG is being used in NIR fluorescence image-guided cancer surgeries and also in the endoscopic marking of colorectal tumors [142].

LIMITATIONS

Nanomedicine for cancer therapy has displayed notable advantages including selective targeting, enhanced anticancer activity, and a decrease in off-target toxicity. A variety of nanoparticles is already in various phases of clinical trials and is further progressing. However, the use of nanoparticles for cancer therapy still has certain limitations and challenges that need to be addressed.

Nanomaterial toxicity especially by metal nanoparticles is one of the considerable shortcomings [143]. The increased rate of reactive oxygen species caused by the nanomaterials can damage healthy tissues and lead to the activation of several defense mechanisms which may likely cause some serious health issues [84]. Studies show that exposure of mesothelial lining to carbon nanotubes induces asbestos-like inflammation and the formation of lesions in mice [144]. Another research revealed that the administration of high doses of nanoparticles led to the toxicity of kidneys and liver to some extent [145]. Sometimes, nanoparticles that enter the system tend to accumulate in the cells, tissues, or even liver rather than getting excreted which might cause damage or trigger immune responses that can lead to other illness [106]. On the contrary, histopathological studies show that some nanomaterials do not cause any toxicity in animals and moreover there is no definite proof that human toxic reaction is particularly induced by the nanomaterials. Hence the topic of nanomaterial toxicity still remains dubious and requires further investigation [12].

Another main drawback in this field is the lack of a suitable tumor model that can fully mimic all the aspects of human cancer [34]. Most of the preclinical studies involve animal models like mice but they lack the intricacies of human tumors and additionally various cancer cell lines are also widely used to assess the anticancer activity of the nanoparticles but these cell lines are homogeneous populations although human tumors consist of many different types of cells in the same tumor [146]. Even though the EPR effect is observed in humans it varies from one cancer to another or even varies between different tumors [147]. Also, EPR is inconsistent in cancer patients than in animal models [34]. This is due to the lack of sufficient experimental data on the EPR effect [35]. Most of the formulations that work on mice or animal models might not work on humans and also the side effects may not be predicted in an animal model but can reflect in humans [146].

The progress in this field led to the development of complex formulations of nanomedicine which pose additional challenges. Complex nanoformulations are difficult to scale-up compared to simple nanoformulation since they add extra steps and modify the already existing manufacturing procedure [34]. Although scaling up of small, simple nanoparticles can be achieved, they are also limited by the problem of batch-to-batch variation during the manufacturing processes and additionally high cost because of the usage of expensive instruments [148]. Also, many nanodrugs fail in their late-phase clinical trials due to the lack of standard protocols [149].

Despite having a low toxic profile and displaying enhanced antitumor activity in a variety of cell lines and multiple animal models, the effectiveness of most approved nanomedicine or nanodrug formulations for cancer therapy did not turn out as anticipated. The results were unsatisfactory since these nanomedicines, when compared to regular therapies, had only a moderate impact on the patient's overall survival [150].

CONCLUSION AND FUTURE PERSPECTIVES

The objective of nanomedicine is to replace or enhance conventional cancer therapies that display poor specificity, limited targeting, and off-target toxicity. A significant amount of research has been done and they show that nanoparticles are already capable of overcoming almost all the limitations of conventional therapies and show great ability for use in targeted cancer treatment. However, this isn't enough since there are still many setbacks that need to be addressed and thoroughly investigated. The field of nanomedicine is mainly embracing the positive side of it but slightly fails to focus upon the many challenges associated with it.

The research on understanding the fundamental concepts of tumor biology, pathways, and processes must continue and novel biomaterials and methods in improving the efficacy of nanomedicine have to be explored to overcome the problems associated with the high cost and scaling up. A joint effort between the researchers, physicians, regulatory bodies, and industries is also needed in order to enhance the clinical translation of cancer nanomedicine. Further investigation should be done in understanding the variable nature of the EPR effect and nanoparticle behavior in the tumor tissue. It is also suggested that researchers must aim at a "disease-driven" approach rather than a "formulation-driven" approach for developing nanomedicine in order to improve its clinical outcomes [151]. The selection of clinically relevant tumor models for assessing nanomedicine is also an important criterion for the long-term progress of nanomedicine. Studies show that Plant-derived tumor explant and

genetically engineered mouse models or GEMM are able to precisely represent human tumors [151]. It is also essential to examine the long-term risks and toxicity associated with nanomedicine on both humans as well as the environment.

In summary, it is clear that the field of nanomedicine is rapidly emerging and a considerable amount of research has been done. Even though there are several challenges in the development of cancer nanomedicine, besides they exhibit attractive properties and there are a lot of potential for nanoparticles in targeted cancer therapy and diagnosis. With a much deeper understanding and extensive research, the challenges can be overcome and it is expected that in the near future cancer nanomedicine will revolutionize targeted cancer therapy and diagnosis and will successfully improve the patient's recovery, survival, and quality of life.

ACKNOWLEDGMENT

Authors thank B.S Abdur Rahman Crescent Institute of Science and Technology, Chennai, India

CONFLICT OF INTERESTS

There is no conflict of interest.

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