Review article

Application of Nano-Particulate Drug Delivery Systems to Deliver Therapeutic Agents into Cancer Cells

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Background

Cancer is a disorder where a group of cells grows uncontrollably, ignoring the physiological rules of cells division. Since its discovery (although the word cancer was not used)3000 BC, extraordinary research aims to uncover novel therapeutic strategies for combating it. Currently, over 60% of clinical trials over the globe focus on cancer. The type of cancer, site, and stage of progression are among the factors determining the treatment selection. Traditional treatment approaches include chemotherapy, surgery, radiation, and radiation-based surgical knives. Side effects associated with traditional therapy highlights the need for novel cancer treatment. Nanotechnology is widely investigated and utilized to treat cancer, where nanoparticles have had a vital role in delivering anticancer medication. Nanoparticle-based drug delivery provides several advantages over conventional drug delivery, including enhanced biocompatibility, stability, permeability, and retention effect, as well as precision targeting. It has also been proven to tackle the resistance to anticancer drugs by targeting the underlying mechanism (drug efflux transporters overexpression, imperfect apoptotic pathways, and a hypoxic environment), enhancing multidrug resistance reversal. Moreover, nanoparticles' role in immunotherapy is undergoing investigation due to their essential role in treating cancer. The current article highlights the role of NP in delivering a chemotherapeutic medication, targeted treatment, and the mechanisms of targeting.

Introduction

Finding novel cancer therapies is a big challenge worldwide [(1)]. The therapeutic efficacy of various malignant tumors has improved significantly with increasingly diverse methods for treating cancer. Chemotherapy is a well-known and extensively utilized approach to cancer treatment. Chemotherapy stops tumor progression by inhibiting cell division and apoptosis enforcement; it kills aggressively developing cells without discrimination resulting in significant side effects, including bone marrow suppression, alopecia, adding to gastrointestinal problems [(2,3)].

Chemotherapy includes Alkylating agents, Antimetabolites, Anthracyclines, Topoisomerase inhibitors, and Mitotic inhibitors. Alkylating agents were among the earliest anticancer medicines, and they are still among chemotherapeutic treatments used widely nowadays. They are directly acting on DNA, resulting in DNA strand cross-linking, incorrect base pairing, or breaks in the DNA strand, which prevents the cell from dividing [(4)].

Antimetabolites drugs are analogs of normal metabolites, and hence incorporation, within normal metabolic processes within cells prevents the synthesis of DNA, RNA, and cell division [(5)]. *Anthracyclines* are anti-tumor antibiotics targeting DNA, affecting cells at all stages of the cell cycle.

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They are effective against a variety of cancers [5]. Topoisomerase inhibitors interfere with the topoisomerase enzymes (I and II), which regulate DNA structural alterations. Topoisomerase inhibitors prevent the cell cycle's ligation phase, which causes DNA single- and double-strand breaks, resulting in apoptotic cell death. They are ideal for treating leukemia, ovarian, gastrointestinal, and lung cancers [5]. Mitotic inhibitors (plant alkaloids) bind to tubulin, preventing microtubule formation and metaphase arrest [5].

New treatment approaches include hormone-based therapy, immunotherapy, dendritic cell-based immunotherapy, antiangiogenics, and stem cell treatments. Hormonal treatment is effective in treating cancer, overcoming cytotoxicity associated with chemotherapy. Advancements in molecular biology uncover its role in cell growth and the regulation of tumor cells. Twenty-five percent and forty percent of tumors with a hormonal basis are reported in men and women, respectively. [6]. Steroids are hormones in nature, are used to treat various tumors, including lymphoma, leukemia, and multiple myeloma. Additionally, they are used to relieve nausea and vomiting after chemotherapy [7].

Angiogenesis inhibitors (antiangiogenic) are chemical inhibitors that block tumor cells' blood supply [5]. They are classified into direct and indirect inhibitors. Angiostatin, endostatin, arrestin, canstatin, tumstatin, and other direct endogenous angiogenesis inhibitors are fragments produced during proteolysis of different ECM components. They stop vascular endothelial cells from multiplying and migrating in response to VEGF, bFGF, IL-8, and PDGF, among other angiogenesis inducers. Indirect angiogenesis inhibitors often impede or stop the production of pro-angiogenic proteins [8].

Side effects of traditional therapy accompanied by emerging resistance to a certain anticancer drug class highlight the need for novel approaches to treat cancer. Oncolytic virotherapy, genetic manipulation of apoptotic and tumor-attacking pathways, antisense, and RNAi approaches are all examples of innovative tactics to treat malignancies. These approaches are used to treat the head, cerebrum, neck, lung, breast, pancreatic, liver, kidney, prostate, ovaries, pancreatic, liver, and skin [9-10].

Most cancer-related research in recent decades has focused on novel drug discovery that more precisely targets tumor cells than normal cells. Despite the advances and the significant progress in targeted therapy, numerous inevitable side effects and resistance yet of concern. With cancer being classified as the second leading cause of death worldwide, and many treatments are ineffective. Altogether, it necessitates a novel anticancer drug that provides specificity and tackles the drug resistance to anticancer therapy.

Nanotechnology has become more widely employed in medicine in recent decades, with applications in diagnostic imaging, nano-sensor diagnostics, tissue engineering, therapy, vaccine delivery, and tumor targeting that are safer and more successful [11-13]. Nanotechnology could expand the area of drugs encapsulation and attachment to biomacromolecules, including proteins and mRNA, improving the efficiency of therapy by incorporating multiple active ingredients that deliver to a certain target to tackle drug resistance and biological barriers. Additionally, it could be employed to link anticancer active ingredients to imaging molecules to achieve a real-time assessment of the drugs' efficacy in vivo, develop new approaches to synthesize vaccines, and improve cancer diagnostics and imaging using scaled-down medical devices [14-15].

There are several advantages that nanotechnology (NP)-based drug delivery systems exhibited in cancer treatment, including excellent pharmacokinetics, tumor cells targeting specificity, reduced adverse effects, and combat drug resistance [16-17]. Traditional chemotherapeutic medicines and nucleic acids are among the drugs found on the interior of the nano-carriers, indicating

that they may be used for both cytotoxic and gene therapy [18].

In medicine, nanotechnology has inaugurated a state-of-the-art era in treating cancer. This intersection necessitates further investigation. The current review outlines the fundamental concepts of cancer therapy based on using the nano-carrier system, highlighting existing challenges, and adding to future research prospects.

Nano-carrier system in cancer therapy

In recent years, there has been an increase in either marketing the nanotherapeutics or those who entered the clinical trial. In 2010, the first phase I clinical study in solid tumors was conducted using a targeted NP-based method, where a small interfering RNA (siRNA)was delivered [19]. NP medicines have been used in cancer immunotherapy, ablation treatment, gene therapy, and chemotherapy [20-21]. It appears to improve immunotherapy and counteracts the immunosuppressive milieu seen in tumors [22].

In anti-tumor multidrug resistance (MDR), NPs have demonstrated some advantages since they provide platforms for drug combination treatment and block the activity of various resistance pathways, such as efflux transporters [23]. Nanoparticle-based treatment can overcome MDR in various malignancies, including breast cancer [24], ovarian cancer, and prostate cancer [26-27].

The size and properties of NPs utilized in drug delivery systems are generally developed depending on the pathophysiology of malignancies. Nanoparticles could provide a substrate for encapsulation to deliver poorly soluble agents into circulation [27-28]. Own to their size and surface features and their role in enhancing permeability and retention, they can extend the half-life of medicines, promoting their cumulation in the target site [29-30].

Unlike classical anticancer therapy, NP possesses distinctive characteristics that overcome high drug concentration and lack of specificity [31]. NPs are tiny compared to biological macromolecules, with tens of nanometres (nm) diameter, rendering them 100 - 1000 times smaller than a single cancer cell, displaying superior intracellular uptake, making them suitable for delivering anticancer medication [32-33]. Nanomaterials are engineered with a maximum size of 200 nm to benefit from the circulatory system, transport to the target to deliver the active compounds and other drug molecules. The increment in drug loading volume is favorable in delivering anticancer. Also, the effectiveness of drug delivery might be enhanced by binding to specific targeting ligands [31].

To achieve their therapeutic purpose, NPs must have high bioavailability, stability, and compatibility with the active compounds used to bind and transport them. Furthermore, NPs should provide selectivity and specificity and release the load upon reaching their target site. The physicochemical properties of the nanoparticles can largely affect the characteristics mentioned above [34]. In comparison to free doxorubicin, the-loaded PEGylated liposomes appeared to reduce cardiotoxicity [35]. Also, in contrast to solvent-based taxanes, NP albumin-bound paclitaxel had fewer adverse reactions and greater tolerable dosages [36].

NP medicines have been used in cancer immunotherapy, ablation treatment, gene therapy, and chemotherapy [20-21]. The nanoparticle-based medication delivery method improves immunotherapy and counteracts the immunosuppressive milieu seen in tumors [22]. It has been found that targeted polymeric NPs carrying docetaxel (DTXL) had better anticancer activity than a solvent based DTXL formulation [37]. The innovation of hybrid nanoparticles has made greater progress; they integrate the characteristics of several NPs to improve the functionality and stability of each drug delivery system [38].

Types of Nanoparticles

Numerous nanoparticles have been developed with different drug targeting technology to achieve a proficient delivery system for diagnosis, adding to its therapeutic

usage (Figure 1). Organic and inorganic NPs have been studied extensively for this purpose [39].

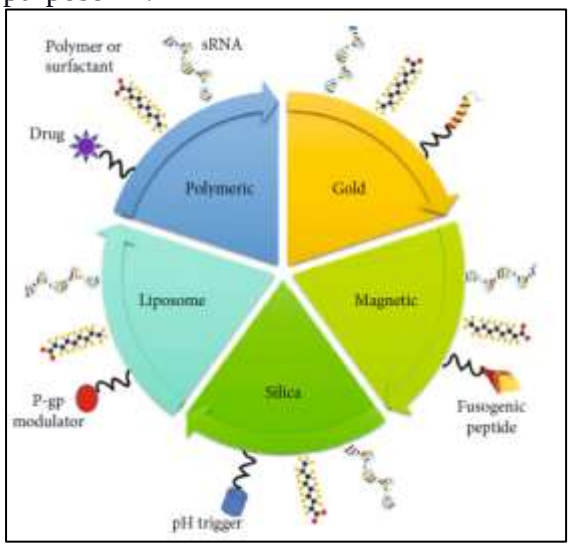

Figure 1. Common drug targeting technology (Zhou *et al*.,2018).

I. Organic NPs

Liposomes based Nanoparticles

Since their first discovery in 1963, liposomes intensively studied as vehicles for drug delivery. Liposomes are synthesized from cholesterol and phospholipids, with self-assembling properties. The amphipathic nature renders their importance for drug delivery. This characteristic facilitates binding to hydrophilic and hydrophobic compounds, encapsulates water-soluble composite in their center, and non-polar medications in their bilayer coating [40-41]. Furthermore, liposomes possess several advantages, including biocompatibility, biodegradability, lacking toxicity or immunogenicity. Additionally, Food and Drug Administration (FDA) already approved liposome-based delivery systems for treating cancer [42-43].

Polymer -based Nanoparticles

Polymeric nanoparticles have been considered as efficient as vehicles for the sustained release of medications. Their usage for controlled release-related purposes studied extensively since the early 1970s; in the 1990s, polymeric NPs that were produced exploiting polylactic acid (PLA) and lactic-co-glycolic acid (PLGA) were explored and depicted as long-circulating [44-45].

Over the last few years, both synthetic and natural polymers have been investigated in targeted drug delivery. Polyhydroxyalkanoates (PHAs) and PLGA have been explored with anticancer medications, including paclitaxel, doxorubicin [46-49], and cisplatin [49-51].

II. Inorganic Nanoparticles

The surface area to volume ratio of inorganic NPs is larger than that of organic NPs. Inorganic NPs features a versatile surface conjugation chemistry that can be easily changed and a simple production process. Gold nanoparticles (AuNPs), carbon nanotubes (CNTs), quantum dots, silica NPs (SNPs), and magnetic NPs (MNPs) are among the nanoparticles that have been researched in drug delivery systems [52].

Gold nanoparticles received great attention in cancer therapy where mixed monolayer-protected masses with gold core are considered potential candidates; moreover, enhancement of drug accumulation in cancer and defeating drug resistance have been shown with AuNPs [53-54]. Gold nanoparticles are also included in immunotherapy, photothermal therapy, and gene therapy [53; 52; 20].

Utilizing gold nanoparticles as a heat source has many advantages compared to conventional hyperthermia. Only the adjacent site to the nanoparticles is affected by heating without damaging the normal cells and tissues; over a short period, the temperature used is drastically higher. Altogether, these properties achieve targeted action, minimizing the drawbacks of traditional methods [55-56]. The heating of the adjacent areas was observed when internal gold nanoparticles performed an external radiofrequency electric field. Thus, they serve as prospective candidates for radiofrequency hyperthermia. The latter could provoke cell death in various tumors; however, high pain levels are a serious drawback. That is why gold nanoparticles were investigated for use in radiofrequency hyperthermia in vitro, employing numerous cell lines [57-58].

Alloy nanoparticles are another type that exhibits structural properties different from their bulk samples. Since Ag has the highest electrical conductivity among metal fillers and, unlike many other metals, their oxides have relatively better conductivity, 2Ag flakes are most widely used. Both metals influence the bimetallic alloy nanoparticle's properties and show more advantages over ordinary metallic NPs [59].

Carbon nanotubes possess unique physical, biological, and chemical characteristics used to deliver numerous anti-cancers to patients suffering from various cancers; these include doxorubicin, paclitaxel, and methotrexate siRNA [60]. Meanwhile, when carbon nanotubes are subjected to nearby-infrared emission, they generate heat, using thermal ablation for cancer therapy [61].

Mesoporous silica NP carriers are a subclass of silica nanoparticles suitable to deliver medication. They can encapsulate the highest quantity of anticancer medications due to the huge internal pore volume, and the supermolecular components operate as a lid, permitting drug cumulation and discharge [62-65]. Silica nanoparticles are among the supreme vehicles for delivering medication due to their improved pharmacokinetics, treatment efficacy, and high stability [66-67]. Additionally, porous silicon nanoparticles have demonstrated significant immunotherapeutic potential due to their immunoadjuvant features, including stimulating antigen cross-presentation, cell polarization, and interferon- (IFN-) secretion [68].

Magnetic Nanoparticles (MNPs) that are purposed in drug delivery consist of metal or metal oxide nanoparticles. Organic materials such as polymers and fatty acids are usually used in coating to improve the stability and biocompatibility of the MNPs. High efficacy in chemotherapy and gene therapy was achieved in treating cancer [69-70]. Additionally, thermal ablation of tumors was achieved by magnetic hyperthermia, offering an alternative cancer treatment [71-72].

Metal oxides-based Nanoparticles

The metal oxide-based nanoparticles are synthesized to modify the properties of their respective metal-based nanoparticles; for example, In the presence of oxygen at room temperature, iron nanoparticles quickly oxidize to iron oxide (Fe_2O_3), increasing their reactivity. Metal oxide nanoparticles are synthesized mainly due to their increased reactivity and efficiency [7]. The commonly synthesized are Aluminium oxide (Al_2O_3), Cerium oxide (CeO_2), Iron oxide (Fe_2O_3), Magnetite (Fe_3O_4), Silicon dioxide (SiO_2), Titanium oxide (TiO_2), Zinc oxide (ZnO). These nanoparticles have possessed exceptional properties when compared to their metal counterparts [73].

Carbon based Nanoparticles

Carbon-based nanoparticles are those made entirely of carbon [8]. They include fullerenes, graphene, carbon nanotubes (CNT), carbon nanofibers, and carbon black and sometimes activated carbon in nano size [74]. **Fullerenes** (C_{60}) is a spherical carbon molecule made up of carbon atoms held together by sp2 hybridization, with about 28 -1500 carbon atoms from the spherical structure of diameters up to 8.2 nm to form the single-layer and with a diameter of 4 to 36 nm for multi-layered fullerenes. **Graphene** is an allotrope of carbon, a hexagonal network of honeycomb lattice made up of carbon atoms on a two-dimensional planar surface. The graphene sheet thickness is around 1 nm [74]. **Carbon Nano Tubes (CNT**), a graphene nano foil with a honeycomb lattice of carbon atoms, is wound into hollow cylinders to form nanotubes of diameters as low as 0.7 nm for a single-layered and 100 nm for multi-layered CNT with varied length (from few micrometers to several millimetres), and open or closed ends (using a half fullerene molecule). **Carbon Nanofiber** is made using the same graphene nano foil as CNT but coiled into a cup or cone rather than a regular cylindrical tube. **Carbon black** Is an amorphous material synthesized from carbon, usually spherical with 20 to 70 nm in diameters.

Agglomerates with 500 nm are formed due to the particles' high interaction [74].

III. Hybrid Nanoparticles

Integrating organic and inorganic NPs in a single drug delivery system enhances the biological features of the multifunctional carrier, improving treatment efficiency while reducing drug resistance [38]. Lipid-polymer hybrid NPs is a promising drug delivery system to treat pancreatic cancer [75], breast cancer [76], and metastatic prostate cancer [77]. This class combines the lipids' biocompatibility with the polymer nanoparticles' structural integrity, enables the encapsulation of hydrophilic and hydrophobic medicines for improved therapeutic impact, and cancer cells can efficiently internalize this system (78) and circumvent the reticuloendothelial system's rapid clearance [79].

Combining organic, inorganic, and hybrid nanomaterials are used frequently in designing NPs. The LSH NPs with a core of silica and a bilayer lipid surrounding are shown to effectively deliver drugs that destroy breast and prostate tumor cells [80]. In vivo, the LSH nanoparticle can be used to deliver paclitaxel and gemcitabine synergistically to pancreatic cancer cells [81].

Kong *et al*. (2015) assembled porous silicon nanoparticles and giant liposomes onto a microfluidic chip to create an advanced nano-in-micro platform. It demonstrated that the co-delivering of incorporated DNA nanostructures and medicines significantly enhanced cell killing of doxorubicin-resistant breast cancers. Additionally, chitosan hybrid nanoparticles and carbon nanotubes appeared to enhance methotrexate anticancer activity in lung cancer cells while decreasing toxicity in normal cells [82]. Additionally, tumor cell death can be enhanced by targeted drug delivery and hyperthermia combination employing manganese and gold as half-shells of metal multilayers and PLGA NPs [83].

Another strategy for nanoparticles design is to combine natural biomaterials and organic or inorganic nanoparticles.; nanotechnology for covering cell membranes is growing and gaining further interest. This method imparts biological features directly onto the NPs by crusting them with cell membranes that are naturally generated, including red blood cells, leukocytes, platelets, bacteria, and cancer cells increasing the efficacy and safety of traditional NPs [84]. Coating nanoporous SNPs by a leukocyte-derived cell membrane can prevent phagocytes clearance of nano-carrier. This feature permits the circulation of the drug for a prolonged period, increasing its accumulation in tumors [85].

Similarly, mesoporous silica NPs encased in cancer cell membranes for cancer therapy enhanced nano-carriers stability and targeting ability [86]. Additionally, the dual-membrane-coated NPs have the potential to improve the function of NPs. Nanoparticles coated with red cells-thrombocyte and red cells-cancer crossbreed membranes improved stability and extended circulation life [87-89]. Furthermore, a multiphase nanoparticle delivery system was proposed for achieving profound tumor infiltration by altering nanoparticles' size and properties at various phases [90].

Metal-organic frameworks (MOFs) or porous coordination polymers (PCPs), which include metal centers and organic connections (Figure 2), have shown considerable interest as a new high crystalline porous substance.

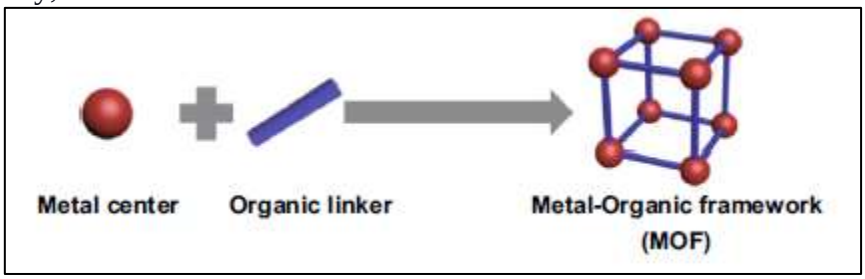

Figure 2. Schematic structure of the MOF (Zhang *et al*., 2020)

Its multi-element structure enables the tuning of the morphology and the microstructures, which renders MOFs suitable for targeted characteristics [91-95].

MOFs can absorb and desorb drugs in a controllable manner [96-97]. In recent years, MOFs have been extensively explored for drug delivery own to their easy functionalization, high drug-loading capacity, virtuous biocompatibility, and biodegradability. Metal-organic framework-based systems attract great attention for attaining a sustained release of drugs [98]. The application of MFO is shown in Figure 3.

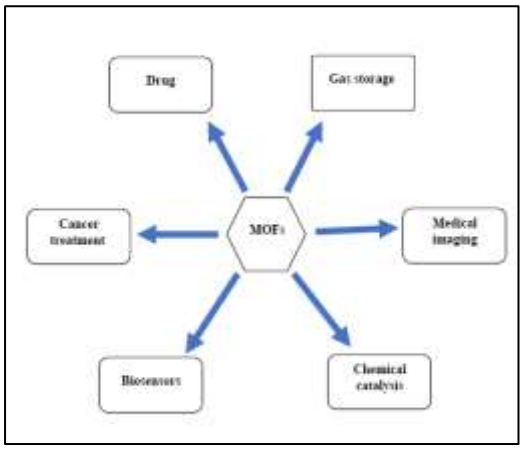

Figure 3. Important applications of MOFs (Butova *et al*., 2016)

Some of the main intrinsic features of MOFs, including compositional versatility, excellent porosity, and tunable crystal size and surface chemistry, have led researchers to use them in biological applications such as the delivery of active ingredients, including drugs biomacromolecules, metals, and gases. It is possible to incorporate active ingredients within the MOFs in several ways [99-102].

MOFs excel many unusual properties in the delivery mechanisms of medicines compared to conventional ones. In addition to its high porosity, special surface, and large surface areas that benefit from improving the efficiency of loading the drugs and molecules, water-solubility, simple functionality, good biocompatibility, and biodegradability could increase the bioavailability and efficacy of drugs. Moreover, medications can be conjugated chemically or encapsulated physically within the transporters via many interactions, such as covalent and hydrogen bonds, π-π effect between aromatic rings, van der Waals forces, electrostatic interactions, etc. [103].

Zeolitic imidazolate framework-8 (ZIF-8) is a subclass of MOFs produced by the incorporation of zinc ions with 2-methylimidazole (Hmim) [104], used to produce a sustained release delivery system for enzymes, DNA, drugs, and fluorescein [105]. It is ideal for constructing a pH-responsive DDS; it is stable at pH 7.4 and degrades in acidic environments [106].

Targeting Mechanism

Targeting cancer cells by nano-carriers increases treatment efficiency while shielding healthy cells from harm, the processes of targeting either passive or active.

In passive targeting, medicines are delivered to the desired site to exert their remedial effect. EPR effect and microenvironments play a key role in the passive nanomedicine targeted approach. However, this targeting has disadvantages, such as non-universal EPR effect, non-specific drug distribution, and variable permeability among different tumor types [107].

Neovscularion and big holes formed in the vasculature due to the high proliferation of cancer cells worsening the permselectivity of cancer vessels than healthy ones (108). Fast and abnormal angiogenesis allows macromolecules, such as nanoparticles, to leak from blood vessels supplying the cancer cells and accumulate within them. At the same time, the deprived lymphatic drainage enhances nanoparticles retention, permitting content release to cancer cells by the nano-carriers. These result in size-dependent EPR effect (one of the primary drivers of passive targeting), where smaller NPs have greater penetrability without leaking into normal ones than larger particles eliminated by the immune system [109-111].

Along with the EPR effect, the tumor microenvironment plays a significant role in passive nanomedicine delivery. Glycolysis

is the primary energy source for cell proliferation, resulting in acidic conditions and lowering the tumor microenvironment pH; accordingly, certain pH-sensitive NPs are activated and release medications in the vicinity of cancer cells [112-113].

In active targeting, cancer cells directly interact with receptors and ligands. This type is suited to proteins and siRNAs, including peptides, monoclonal antibodies, amino acids, carbohydrates, and vitamins [114]. Nanoparticles surface ligands selectively target the overexpressed particles on the surface of cancer cells, distinguishing between targeted cells and the normal ones [115-116]. Receptor-mediated endocytosis that results from NPs ligands - tumor surface receptors interaction allows the successful release of medication by internalized NPs [117]. They are specifically bound to targeted cells receptors, folate receptors, transferrin receptors, epidermal growth factor receptors (EGFR), and glycoproteins, which are widely investigated for this purpose.

Transferrin (one of the serum glycoproteins) that transports iron into cells. Its receptors are found to be overexpressed in most solid tumors. As an active targeting method, transferrin-conjugated NPs are used to deliver medication to treat cancer [118-120]. Transferrin-modified NPs revealed a better cellular uptake efficacy accompanied by intracellular drug delivery enhancement, and transferrin-conjugated polymeric NPs appear to be vital in tackling chemotherapy drug-resistant [121-122].

Folic acid is a vitamin that is vital for the synthesis of nucleotides. Both isoforms of folate receptor (FR), alpha, and beta (α and β) were overexpressed in about 40% of tumors and on the surface of hematopoietic tumors, respectively [123]. Therefore, the FR-targeting method utilizing folate-conjugated- NP is extensively used to treat cancers [124-125].

Various types of glycoproteins are expressed in cancers; these include-immunological proteins, lectins, which distinguish and bind to carbohydrates specifically [126]. Lectins- NP conjugation constitutes a directed lectin-targeted pathway and the reverse targeted pathway of lection, inversely target lectins on tumor cells employing carbohydrates moieties- nanoparticles integration [127-128].

Tyrosine kinase**,** ErbB family includes epidermal growth factor receptor, extensively utilized as a target for cancer therapy [129-130]. EGFR is overexpressed in various tumors and included in tumors growth and progress. The Human epidermal receptor-2 (HER-2) targeting is a popular treatment for HER-2 positive gastric and breast cancers. Consequently, nanoparticles aimed to integrate customized ligands bind to EGFR targeting EGFR-overexpressed tumor cells are a promising approach to deliver drugs [131]. Another approach of active targeting that improves the specificity of active targeting, conjugation of two cancer-specific ligands in a single nanoparticle [132].

Some Nanoparticles directly affect angiogenesis rather than cancer cells. The Vascular Endothelial Growth factor (VEGF) and its receptor VEGFRs -interaction is vital for vascularization, and therapeutic efficacy appeared to be enhanced by VEGFR-2 & 3 targeting by liposomes [133-134].

Integrins (extracellular matrix proteins cell receptors) are vital for the migration and invasion of cancer cells; αvβ3 integrin is essential for the calcium-dependent pathway, which provokes the migration of endothelial cells, found to be overexpressed in tumors neovascularization endothelial cells [135-136].

The therapeutic efficiency of cationic nanoparticles, combined with an αvβ3 integrin-ligand targeting, improved gene delivery to cancer using mice as an experimental model [137]. The efficacy of anti-VEGFR therapy is enhanced via targeting αvβ3 integrin. The latter is correlated with VEGFR-2 signalling and blocks αvβ3- integrin-binding result in VEGF signalling reduction [138].

The Vascular Cell Adhesion Molecule-1 (VCAM-1) is involved in angiogenesis through interaction with vascular

endothelial cells, is overexpressed in various cancers [139], heightening its importance in active nanoparticle targeting. Increased efficacy of VCAM-1 targeted nanoparticles in breast tumors was reported by Pan *et al*., 2013 [140].

The tumor microenvironment components, metalloproteinase (MMP), are included in remodeling the extracellular matrix and neovascularization, and MMP-sensitive NPs were shown to have a prospective anticancer activity in various cancers including melanoma and pancreatic cancer, and breast cancers [141-143].

Conclusion

Cancer is a health concern that attracts the attention of researchers worldwide to find a novel treatment. The need to select various local or systemic therapies is based on several prognostic and predictive factors [144]. Treatment selection and its progress are dependent on the type and the site of cancer and the stage of progression. Nanotechnology constitutes a novel approach to treat cancers. Organic and Inorganic nanoparticles were used to treat several cancers.

Drug delivery systems based on nanotechnology appeared to improve pharmacokinetics, stability, biocompatibility, and tumor targeting, playing a crucial role in minimizing systemic toxicity and tackling resistance to anticancer medication [16,17]. Traditional chemotherapeutic medications and nucleic acids are among the drugs found on the interior of the nano-carriers, indicating that they may be used for both cytotoxic and gene therapy [18]. NP-based drugs are widely employed in targeted therapy, chemotherapy, radiotherapy, gene therapy, and hyperthermia [145,146]. Additionally, it provides better platforms for drugs combination that helps counteract drug resistance pathways.

Hybrid NPs attract more attention in drug delivery with advances in research, showing improved properties over organic and inorganic types. They integrate the characteristics of several nanoparticles to improve the function and stability of each used system [38, 7]. Since its discovery, the metal-organic framework (MOF) has attracted widespread attention. It has been incorporated in bio-imaging [147], catalysis [148], storage of materials [149], sensing [150,151], purification [152], and drug delivery [153,154]. Further studies are required, focusing on the biology of individual cancers for more accurate and directed targeted research, besides design and engineer hybrid nanoparticles that suit cancer therapy to achieve targeting specificity.

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