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REVIEW

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Nanoengineered approaches to improve the efficacy of targeted drug delivery for the treatment of malignancy: a comprehensive review

Jagabandhu Bag[1], Sabyasachi Banerjee[2], Arnab De[3], Sreejan Manna[4], Subhasis Banerjee[2], S. K. Ashok Kumar[5] and Sourav De[6*]

Abstract

Background The second leading cause of mortality in the world, behind cardiovascular disorders, is cancer. The currently employed treatment options including radiotherapy, chemotherapy are reported with many adverse reactions. These limitations in combination with high cost of therapy have restricted the management of malignancy. In this review, several nanocarriers-based approaches were described as effective treatment option of malignancy.

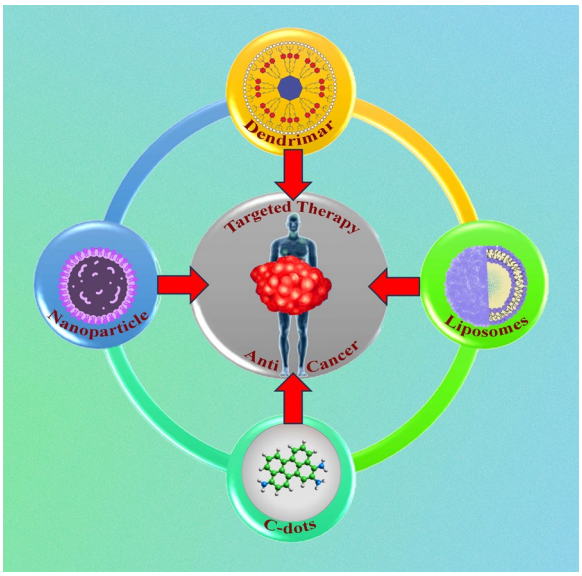
The main body of the abstract The development of innovative and effective targeted therapies for malignancy relies on alterations in the molecular biology of cancerous cells. Given the nonselective destruction of healthy cells, the harmful effects of existing chemotherapy drugs, and the development of multidrug resistance, has thrived the development of novel carriers for improved targeting efficacy of anticancer drugs. The present study offers a comprehensive account of diverse cytotoxic drug carriers, such as carbon nanotubes, liposomes, polymeric micelles, dendrimers, polymeric nanoparticles, and polymeric conjugates, in the context of passive and active targeted cancer therapy. The carriers are known to enhance the permeability and retention or functionalize the surface, thereby improving the efficacy of drug delivery.

Short conclusion The present literature delineates the progressions made in the nanoengineered approach for administering therapeutic agents to the tumour micro-environment.

Keywords Cancer, Nanocarriers, Drug carriers, Tissue microenvironment, Drug delivery

*Correspondence:
Sourav De
chemsouravde@gmail.com
Full list of author information is available at the end of the article

Graphical Abstract



Background

Cancer is a group of disorders that exhibit uncontrolled cellular proliferation, immortality by replication, and refusal to undergo cellular death. Cancer apart from hematologic malignancies, in which melanoma cells proliferate and circulate widely throughout the blood, lymphatic, and bone systems, cells develop into an abnormal cell mass known as a tumour [1, 2]. Proto-oncogenes and tumour suppressor genes are the main targets of damage or mutation in the pathogenesis of cancer. Proto-oncogenes encode proteins that play a crucial role in the regulation of cellular proliferation and differentiations, while tumour suppressor genes encode proteins which generate signalling that is inhibitory for cellular development and/or promote apoptosis. The development of a tumour necessitates alterations in both oncogenes and tumour suppressor genes. Therefore, mutations are more prone to occur in the genes responsible for a group of proteins that regulate DNA damage, referred to as tumour susceptibility genes. The development of cancer is attributed to mutations that are selected clonally, as they promote abnormal and unregulated cell division, lack of mechanisms to hinder excessive cell growth, impeded cellular death and transmissions, accumulation of genetic anomalies, and suppression of cell division [3–9]. Surgery and radiation are considered the most efficacious interventions for treating localized and non-metastatic cancers. However, their effectiveness is limited in cases where the cancer has disseminated to other regions of the body. Currently, chemotherapy, hormone therapy, and biological treatments (living organisms that can modify the immune response) are used to treat metastatic cancers because they can circulate throughout the body and reach all organs [10].

Targeted therapies aim to inhibit biological signalling pathways or cancerous proteins that contribute to the development and advancement of tumours. The therapeutic interventions under consideration are directed towards molecular targets, such as growth factors, receptors, kinase cascades, or molecules associated with angiogenesis and apoptosis. These targets are typically existed in normal tissues, but in the context of cancer, they are either overexpressed or mutated. The forefront therapies strive to obstruct the signals that trigger the uncontrolled proliferation and division of cancerous cells, trigger the programmed cell death of cancer cells, activate the immune system, or administer chemotherapy agents exclusively to cancerous cells, thereby limiting the mortality of healthy cells and circumventing adverse effects [5–10].

By examining the oncological therapies sanctioned by the Food and Drug Administration (FDA) within the last 14 years, it is possible to determine the significance of these new anticancer medications 14 of the 19 anticancer medications such as Vandetanib, Pertuzumab, Lapatinib, Ceritinib, Regorafenib, etc., were authorised between 2000 and 2006 used for targeted treatments [11]. During the period from 2007 to 2012, a notable increase

in the statistical figures. Specifically, a total of 40 drugs were granted licenses for the management of diverse types of cancers, with 30 of these drugs being specifically designed to target cancer cells. It's noteworthy to emphasize that 18 of the 19 cancer medications were authorised by the FDA between 2012 and 2014 focused on inhibiting or blocking certain cancer proteins and/or biological transduction pathways [12–14]. To modify cellular signalling events, it is possible to employ cytotoxic molecules that can be linked chemically to monoclonal antibody or peptide ligands. These molecules can then be directed towards molecular targets that are either overexpressed or solely expressed upon the tumour cell surface. The aforementioned-molecules encompass toxins, cytotoxic agents, radionuclides, and cytokines [15–18]. Small molecule inhibitors are selected based on their ability to hinder the signalling pathways implicated in the anomalous generation of proliferative, anti-apoptotic, and angiogenic actions [11]. To feed the tumour bulk, tumours require additional blood vessels. They are created by the angiogenesis process from pre-existing vessels. Anti-angiogenic treatment is used to reduce tumour blood supply by blocking angiogenesis using drugs like the VEGF inhibitor SU-11246 or bevacizumab, a monoclonal antibody against VEGF, was the first anti-angiogenic drug approved by the FDA [19].

The utilization of chemotherapeutics as drug delivery systems (DDS) to tumour regions has improved significantly owing to the development of flexible materials and a more comprehensive understanding of tumour biology. Specifically, over the last two decades, advancements in nanotechnology have played a significant role in enhancing clinical cancer therapies [20–25]. NP-based DDS or nanocarriers (NCs) have the potential to improve the effectiveness of therapy and selectivity through their impact on the enhanced permeability and retention effect (EPR) in tumour tissues [26–33]. Furthermore, the cellular uptake of NCs surpasses that of traditional chemotherapeutic agents. Liposomes, polymeric nanoparticles, and micelles are among the most utilized types of nanocarriers, as reported in the literature [34a]. Several nanoparticle-based chemotherapeutics have been granted clinical approval such as Adynovate, Zilretta, Rebinyn, Onivyde, Vyxeos, Avinza [34b], while others are currently undergoing preliminary clinical trials. Despite their potential benefits, the industrial scale up of NCs are difficult due to reduced yield, involvement of expensive tools and machineries. The polymeric NCs exhibit many advantages including biodegradability, increased bioavailability and reduced toxicity of the incorporated therapeutic agents. The imperfections pose security risks, particularly in the context of continuous cancer therapy. We have discussed drug delivery NCs for treating cancer in this section. The topic of nanoparticle-based cancer chemotherapy has been explored more thoroughly, with particular emphasis on its application in the treatment of colon, lung, and female malignancies.

Main text

Nanocarriers in cancer therapy

The physical and chemical characteristics of NPs have a significant impact on their efficacy. Nanoscale molecules have been synthesized using a variety of materials, including synthetic lipids, proteins, polymers, and inorganic particles [34–42]. They provide drug protection, solubility, and stability, which improves pharmaceutical distribution. NPs are functionalized with target-specific ligands, including aptamers, folic acid, antibodies, and peptides, to facilitate the delivery of drugs to specific sites. The aforementioned benefits result in an extensive variety of drug administration techniques that exhibit enhanced pharmacokinetics and reduced adverse effects, contingent upon the surface physicochemical characteristics and dimensions [43–48]. Liposomes are a type of organic NC characterized by a spherical shape, which consists of a self-assembled phospholipid bi-layer enclosing an aqueous chamber in the interior [38, 49]. The lipids for liposome NPs that are commercially accessible include phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine. Liposomes are intriguing because they allow for drug transfer across cellular membranes and are less-toxic, making them simple for cancer cells to internalise. The main downsides of this approach are their exorbitant preparing procedures, reduced loading of drugs and stability, and rapid physiological breakdown before any therapeutic effect. The first nano-based pharmaceutical sanctioned by the United States FDA was Doxil®, a liposomal nanoparticle formulation of doxorubicin. This chemotherapeutic agent is predominantly employed in the treatment of breast cancer (BCa), acute lymphocytic leukemia, and bladder cancer. The formation of liposome (polyethylene glycol) provides long circulating properties [63–67]. ThermoDox® is the only thermosensitive liposomal (TSL) under development; it is a doxorubicin-containing TSL formulation. This formulation responds to temperature over 40 °C and selectively releases its payload in the tumour microenvironment, enhancing the anticancer activity of its loaded drug [50]. Lipid-based NCs are more effective in reducing drug release than liquid oils, allowing for controlled drug release [51]. Solid lipid nanoparticles (SLNs) are commonly utilized as intravascular distribution NCs for drugs due to their ability to encapsulate drugs within a hydrophobic lipid core. Polymeric micelles are another naturally occurring lipid-based NP with a size of less than 100 nm [52, 53].

The amphiphilic nature of polymeric nanoparticles, characterized by a lipophillic core and a lipophobic shell, renders them highly suitable for drug delivery applications involving compounds with restricted water solubility. Reverse micelles (RMs) are commonly employed owing to their high dissolving capability in oil phase [54–56]. However, RMs have inability to coordinate the delivery of targeted drugs and their lack of tissue selectivity [55]. Epigallocatechin-3-*O*-gallate (EGCG), a polyphenol with anti-inflammatory effects, is the primary component of the micellar nanocomplex (MNC) NPs [57]. Protein medicines can be protected by MNCs from proteolytic enzyme action while being transported to the cancerous tissues (Fig. 1).

Genexol-PM®, a paclitaxel (PTX)-loaded micellar formulation based on amphiphilic polymers, is used to treat metastatic breast and small-cell cancer. The formulation boosts the anticancer efficacy of drugs, since it has prolonged circulation time as for the polymer coat prevented the rapid elimination of the drug [58]. An organic linker and a metal ion or spacer make up the class of porous NPs known as metal–organic frameworks (MOFs), which have different hybrid topologies [59]. MOFs exhibit favourable characteristics such as higher surface area and controllable pore size, rendering them as potential contenders for the purpose of regulated drug delivery. However, in order to utilize MOFs as carriers of anticancer drugs in vivo, it is imperative to decrease their size to the nanoscale. Nano-MOFs are particularly valuable in the pharmaceutical industry because they enable controlled drug release [60, 61]. The nano-MOFs can encapsulate higher drug content in comparison with conventional porous materials for treatment of cancer. Stimuli-responsive systems based on MOFs have been developed in response to various stimuli such as redox-based reactions, pH, magnetic fields, ATP, temperature, irradiation, pressure, and humidity [62]. Despite the fact that most of the NCs approved by the FDA utilize passive targeting via EPR, some of the latest generation NCs currently undergoing clinical trials employ active targeting strategies due to recent progress in protein engineering and polymer chemistry.

Targeted delivery of anticancer drugs via NPs

In order to provide better chemotherapy, the medications must first pass through biological barriers before being localised just in the tissues of the target tumours. This results in increased anticancer effectiveness with a minimum amount of off-target adverse effects. A common strategy is drug targeting using passive and active NPs [68, 69]. With passive targeting, NCs use the physio-pathologic characteristics of the tumour, such as the tumour vasculature, to passively locate their loaded anticancer medications in tumour tissues. Poor lymphatic drainage and severely flawed tumour vascular architecture result in an increased permeability and EPR impact [70, 71]. Furthermore, the use of defective tumour vasculature and tiny NCs is employed for passive targeting of anticancer medications [72]. In the microenvironment of cancer tissue, the endothelium of the blood arteries exhibits greater gaps (100 nm–2 μm), which makes them different from normal blood vessels.

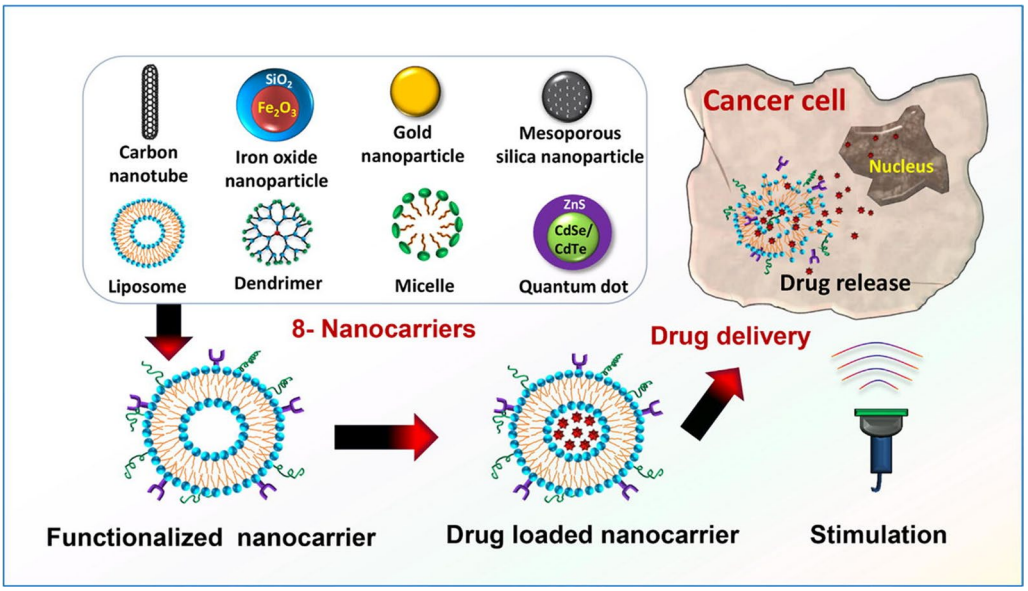


Fig. 1 NC-based drug delivery systems for cancer therapy (adopted with permission from Hossen et al., 2019) [168]

As a result, tumours may be easily reached by NCs in this size range, allowing for the specific localization of medications within tumours [73, 74]. Moreover, tumour tissues have a compromised lymphatic system, which causes their centres to have higher interstitial pressure than their peripheries. This subsequently enables NCs to access the interstitial zone, where they stay for a longer duration and eventually enhance the anticancer effect in tumours [75]. By developing long-lasting NCs, anticancer medications can also be passively targeted. NCs have an extended interaction with biological systems and are often able to traverse the tumour microenvironment, resulting in increased therapeutic effectiveness of the drugs they transport against cancer due to their prolonged retention in the human system. Cationic NCs are also used to localise their loaded drugs in tumours in a manner similar to that, whereby they engage electrostatically with angiogenic endothelial cells in tumour blood vessels [69, 70].

NCs surfaces modified with a targeting moiety are used for active drug targeting. The surface of NCs can be functionalized with a targeting moiety, which enables the identification of a malignancy-specific antigen or receptor. Pharmaceutical agents are designed to exhibit selective targeting towards the intended site of action, thereby limiting their absorption into non-targeted healthy cells and tissues. Moreover, certain targeting ligands have the ability to initiate the mechanism of receptor-mediated endocytosis, thereby facilitating the liberation of drugs from NCs within the confines of specific cells [76]. Receptor targeting is a successful strategy for more effective chemotherapy that involves drug tumour internalisation [77]. Cancer cells exhibit an over-expression of multiple receptor types, which facilitates the binding of targeting moieties to these receptors. This, in turn, enables the localization of drugs with a high degree of specificity to malignant cells [78, 79].

The responsiveness of drugs to various stimuli such as hyperthermia, pH, redox potential, and specific enzymes present in the cancer microenvironment results in their liberation from NCs in proximity to tumours. Similarly, NCs are designed to respond to changes in the cancer microenvironment [69, 70]. With better chemotherapy, higher concentration of drug is thereby obtained in the tumour microenvironment. A major global cause of cancer-related mortality is lung cancer (LCa) [80]. The treatment of cancer, specifically squamous cell carcinoma or adenocarcinoma, typically involves a chemotherapy regimen consisting of a combination of two or three chemotherapy agents. These agents may include docetaxel (DOX), cisplatin, Abraxane®, PTX, gemcitabine, vinorelbine, and pemetrexed [81]. Metallic NPs possess the potential to penetrate the vasculature and tissues of malignant cells, making them a viable option for drug delivery systems that can mitigate the harmful effects of cytotoxicity on healthy cells. Ramalingam and colleagues used polyvinylpyrrolidone to conjugate Dox onto gold NPs using non-organic methods [82]. The NPs exhibited anti-proliferative effects on the A549 human lung cancer cell line, while also stimulating the production of reactive oxygen species (ROS) within the cells and promoting cell death. Similar to this, Kalaiarasi and colleagues created copper oxide NPs that might induce apoptosis in A549 cells by downregulating certain oncogenes, such as histone deacetylase [83a]. Even though platinum (Pt)-based anticancer drugs have been utilised extensively for LCa, their clinical effectiveness has been severely hindered by unpleasant side effects such as lack of selectivity, high systemic toxicity, and drug resistance, seriously limit their clinical application and drug resistance [83b]. To get around these issues, Pt(II)-loaded drug NCs have been created. For instance, Tsai and colleagues developed self-assembling NPs containing diaminocyclohexane-Pt(II) (DACHPt) that exhibit high absorption rates in LCa cell lines that are insensitive to platinum (Pt). The resulting tumour toxicity is significant [84]. In order to tackle multidrug resistant LCa, DACHPt-loaded NPs provide a unique, powerful system for NCs. Drugs or NCs can be combined through targeting cells, specifically molecules including peptides, ligands, aptamers, and antibodies, that can differentiate across cancerous and healthy cells, to accomplish active targeting. Song and colleagues developed core–shell lipid-polymer hybrid nanoparticles (LPNs) with epidermal growth factor (EGF) conjugation to actively transport DOX and resveratrol to cancer cells [49]. The synergistic tumour suppression and low off target effects of the biodegradable EGF-DTX/RSV-NPs highlighted their potential for LCa therapy.

Vitamin E succinate-based NCs exhibit biocompatibility, hydrophobicity, simplicity in manufacturing, and anticancer efficacy. Nevertheless, hyaluronic acid (HA), an anionic polysaccharide that is bio-degradable and bio-compatible, allows the active targeting of cell surface adhesion receptors (CD44) on cancer cells. Song et al. developed redox-sensitive NPs loaded with PTX using conjugates of HA-disulfide-vitamin E succinate. The aim was to enhance the specificity of tumour cell targeting and facilitate targeted drug release [85]. Compared to non-redox-sensitive NPs and paclitaxel monotherapy, the redox-sensitive nanoparticles loaded with paclitaxel demonstrated enhanced cytotoxicity in both A549 cell lines and A549 animal xenograft models. The MTT assay showed a maximum of 70.5% apoptosis for PTX incorporated HSV NCs. The study reflected 75.4% in vivo antitumour efficacy of PTX incorporated HSV NCs in respect to

Taxol (39.2%) and PTX-HV NCs (55.2%). These findings suggest the potential of redox-sensitive nanoparticles as a targeted delivery system for PTX in the treatment of lung cancer.

The medicinal usage of the flavonoid naringenin (NAR) is constrained by its lower water solubility, stability, and bio-availability. By creating polymeric NPs from biocompatible and biodegradable polymers, these problems might be avoided. Naringenin polycaprolactonenanoparticles (NAR-HA@CS-PCL-NPs), synthesized by Parashar et al., exhibited toxicity to A549 cells but inert to non-cancer cell lines [86]. In vivo, the chemopreventive capabilities of NAR-HA@CH-PCL-NPs were exhibited through the use of urethane-induced LCa rat models. The 26-base G-rich DNA oligonucleotide known as AS1411 has been observed to be over-expressed in various cancer cells. Its primary function is to act as a nucleolin-binding aptamer [87]. A multipurpose NC was made by combining AS1411 aptamers with chitosan conjugated to fluorescent gold nanoclusters loaded with methotrexate, called MTX@AuNCs-CS-AS1411, which Guo et al. found to have considerable anticancer efficacy in A549 cells and to reduce tumour development in BALB/c mice [88]. To combat drug resistance during LCa therapy, it is effective to co-deliver functionally separate anticancer medicines. Amreddy et al., created polyamidoamine (PAMAM) dendrimers attached to folic acid to deliver cis-diamine Pt and human antigen R (HuR) siRNA to LCa cells that exhibit overexpression the folate receptor-alpha [89]. The enhanced HuR in LCa cells was the reason why the dendrimers were nontoxic to normal lung fibroblasts while having stronger therapeutic benefits than the individual treatments alone. By targeting DNA methyltransferases, miRNA-29b prevents DNA methylation in LCa cells, which further prevents cell growth and death. A nanocarrier system could be able to lessen its drawbacks, such as off-target effects, degradation, and inadequate cellular absorption. A transmembrane protein called MUC1 that is overexpressed in LCa makes it easier to actively target medications to the tumours.

A nanocarrier system might reduce issues including off-target effects, degradation, and inadequate cellular absorption. A transmembrane protein called MUC1 that is overexpressed in LCa makes it easier to actively target medications to the tumours. In order to deliver miRNA-29b to LCa tissue in vivo, Perepelyuk et al., developed mucin1-ap loaded NPs which showed improved stability and prevented tumour development [90]. The distribution of NPs by inhalation to enhance tumour targeting is a newly developed field in the treatment of lung cancer. After intratracheal delivery, Mice have been shown to tolerate PTX-polyglutamic acid conjugates well, and Dox NPs inhaled demonstrated less cardiac adverse effects than the same traditional dose of Dox [91]. As per research conducted in this domain, inhalation of lipid-based NPs leads to an increased incidence of tumourigenesis and prolonged retention of the same in the lungs. It is potential that these and other inhalation-based NCs will be used to deliver anticancer medications in the future, particularly to lung malignancies. The field of pharmaceutical nanotechnology has witnessed significant progress in recent times, facilitating the development of surface-engineered intelligent NP systems. These systems are designed to deliver chemotherapy drugs with high precision to malignant cells. In a current investigation, homoharringtonine was administered to lung cancer cells utilizing a PLGA-based dual-functionalized nanoparticle surface that was designed with an EGFR aptamer. The NPs exhibited targeted drug delivery to LCa cells by virtue of their ability to recognize receptor/s and response towards the existing glutathione in the surrounding microenvironment [92].

Drug-carrying dendrimers

Dendrimers are molecular entities characterised by their nanoscale dimensions, with a radially symmetric structure that exhibits a high degree of uniformity and homogeneity. These molecules generally consist of a centrally located core, surrounded by inner and outer shells, which contribute to their well-defined and monodisperse nature. Various categories of dendrimers exist, which are contingent upon the pliability of the ligand and central core. The anti-neoplastic efficacy of the most widely employed dendrimers for pharmaceutical conveyance is also noteworthy (Fig. 2).

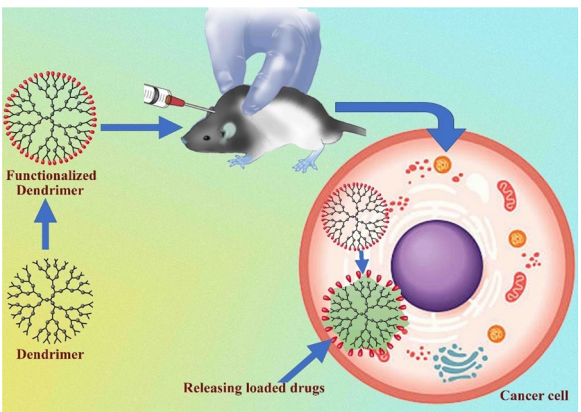


Fig. 2 Dendrimers as agents for drug delivery in the context of cancer treatment

PAMAM dendrimers loaded with doxorubicin and PTX

Lai et al. introduced a polyamidoamine dendrimer chemical for the treatment of cancer that contained DOX and was coupled with amide and hydrazone [93]. In a study on drug release, PAMAM-hyd-DOX NCs released the drug more quickly at 4.5 pH (47% in 24 h) than they did at 7.4 pH (8% in 24 h), but PAMAM-amide-DOX released drugs more slowly at 4.5 pH. PAMAMhyd-DOX NCs is also more dangerous to cancerous cells than PAMAM-amide-DOX NCs, according to cytotoxicity. Wen et al. looked at how well a PAMAM dendrimer with pH-sensitive multi-walled carbon nano-tubes released DOX under controlled conditions [95a]. Wang et al. investigated dendrimers coupled with folic acid to target cancer cells [95b]. According to a drug releasing experiment, the as-prepared NCs released DOX more slowly at 7.4 pH (19% in 4 h) than they did at 5.0 pH (22% in 4 h). KB cells are more resistant to DOX-loaded dendrimers (22%) than to blank dendrimers (90%) in terms of cell viability. Lee et al. studied dendrimer and duplex oligodeoxynucleotide bioconjugates and evaluated the efficacy of DOX administration to fight breast cancer [95].

Rompicharla et al., created a PEGylated PAMAM dendrimer that is loaded with PTX and functionalized with biotin to treat lung cancer. The results of the investigation into cell viability suggest that the PAMAM-PEG-PTX-biotin platform has enhanced efficacy against cancer cells in comparison to free PTX. Specifically, the recorded viability rate of the PAMAM-PEG-PTX-biotin platform after 48 h was 50%, while the viability rate for free PTX was 74%. This difference was especially pronounced at lower drug doses of 3.125 µg/ml. Greater drug concentration (50 µg/mL) the findings were further boosted using free PTX and the PAMAM-PEG-PTX-Biotin platform, which increased the results by 50% and 15% in 48 h, respectively [96]. For the purpose of cancer therapy, Majoros et al., created PAMAM NCs with folic acid, fluorescein isothiocyanate, and PTX (a chemotherapeutic medication). At a dose of 200 nM, free PTX, and FI-FA-PAMAM-Pac NCs demonstrate comparable resistance to cancerous cells, according to an optical density analysis. Gel permeation chromatography (GPC) indicates that the original average molecular weight of PAMAM is 26,892 g/mol, and after conjugation, it rises to 43,110 g/mol [97].

pH dependent drug targeting

Targeting the solid tumours' intracellular organelles and acidic extracellular milieu, pH-triggered administration is thought to be numerous stimuli-based targeting methodologies. Review concentrates on the chemistry of pH-dependant biomaterials used to create NCs for intracellular and/or extracellular medication release tailored to specific cancer sites. Through different methods, such as protonation, charge reversal, or breaking of a chemical bond, the biomaterials which are pH-responsive caused conformational changes in these NCs, allowing tumour-specific cell uptake or drug release. In order to overcome the difficulties associated with traditional chemotherapy, it would be helpful to better understand these mechanisms in order to build drug delivery methods that are more effective. In order to precisely target the chemokine receptor (CXCR4) based on pH variability between normal and cancerous tissue, Chittasupho et al. produced a DOX embedded LFC131 peptide linked dendrimer, and the release of DOX has an anticancer impact. Drug release research demonstrates the carrier's as-prepared pH-dependant drug releasing profile, for instance at 5.0 pH (13% in 72 h). In comparison to pH7.4, DOX release was quicker (5% in 72 h) [98].

Ligand-based targeting

Utilising homing mechanisms known as ligands, medications that can target tumours specifically while preventing drug access to non-target locations. This encompasses any molecule capable of identifying and adhering to a specific antigen or receptor/s that has been excessively expressed or solely expressed in particular cells or tissue constituents (Fig. 3).

Targeting based on transferrin

A globulin (glycoprotein) called transferrin (Tf) helps the ferric ion (Fe^{3+}) move via transferrin receptors on the plasma membrane. Through receptor-mediated

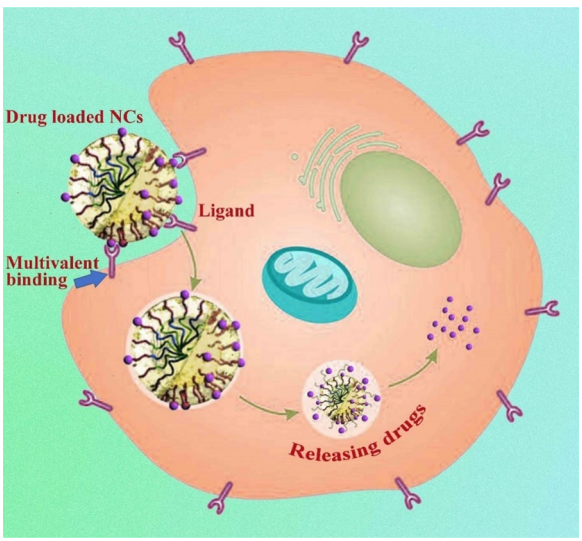


Fig. 3 Ligand-based NCs for targeted drug delivery into tumour cells

endocytosis, Fe^{3+} is delivered intracellularly. In a nutshell, ferrotransferrin is created when two Fe^{3+} ions are securely bound by the iron-free version of the protein, apotransferrin. At neutral pH, the ferrotransferrin surface receptors of the cells bind strongly, and then the ferrotransferrin-bound receptor is exposed to endocytosis [99]. Treatment of several malignancies, particularly breast cancer, is greatly aided by transferrin functioning as ligand. Only the molecular basis for the increased efficacy of PTX-loaded, Tf-conjugated NPs in breast cancer cell lines was investigated by Sahoo et al. The antiproliferative activity of Tf-conjugated NPs was found to be greater and sustained in the MCF-7 human breast cancer cell line at the lowest drug dose (1 ng/mL) compared to free drug or unconjugated NPs (Fig. 4). The enhanced anti-proliferative efficacy of the medication when combined with conjugated NPs can be attributed to their heightened cellular uptake and reduced exocytosis, as compared to unconjugated NPs [100].

The theory is that Tf-conjugated NCs are more effective than unconjugated ones. A considerable proportion of unconjugated NCs that are adopted by the cell undergo rapid exocytosis due to their inefficient release capacity to the cytoplasmic compartment from the endosomal compartment during transit. Following their absorption by TfR, Tf-conjugated NCs could follow a different intracellular sorting pathway than unconjugated NCs via non-specific endocytosis. Conjugated and unconjugated NCs have different absorption and sorting mechanisms, which in turn affects both the intracellular retention of NCs and the therapeutic effectiveness of the encapsulated drug [101].

Targets based on vitamins

The value of employing vitamins as a targeted ligand for medication delivery was emphasised by several research groups. The vitamins folate, vitamin B_{12} (VB12), biotin, and thiamine may be employed as targeting molecules. A variety of tumour cells requires a vitamin folic acid (FA) (M.W.: 441 Da) that is necessary to produce purines and pyrimidines [102].

A subject of current attention is the function of VB12 in treating cancer. For the purpose of producing proteins, cancer cells require the enzyme VB12, which changes homocysteine into methionine. Tumour cells overproduce the VB12 receptor in order to fulfil their biological need for VB12. In order to use VB12 and its receptor interaction for targeted treatment, VB12 is taken in orally by a process called receptor-mediated endocytosis. In this method, the small intestine's intrinsic factor (IF), a protein that binds VB12, initially binds VB12. VB12 is then transported throughout the cell when the VB12-IF complex attaches to an IF receptor present onto the surfaces of intestinal epithelial cells. In an IF-independent manner, it can also be delivered via transcobalamin II (TcII), another VB12-binding protein. It has recently been demonstrated that the oral absorption of several peptides and proteins may be improved by taking advantage of the VB12 uptake mechanism. According to Chalasani et al., VB12 serves as a model molecule for peptide- or protein-encapsulated NP targeting in caco-2 cells. In their investigation, they demonstrated that VB12-modified NPs had a higher amount of uptake, whereas caco-2 cells bind, take up, and transport uncoated NPs to a lesser extent [103]. The cellular absorption of VB12-modified NPs was improved by the addition of IF, but not for uncoated particles. The outcome demonstrates that increased cellular absorption occurs in VB12-modified NPs via IF-dependent or IF-independent processes, with the addition of IF increasing uptake to a lesser amount. Further research has been done on the potential effectiveness of a peptide- and protein-tagged VB12 carrier system for oral administration [104].

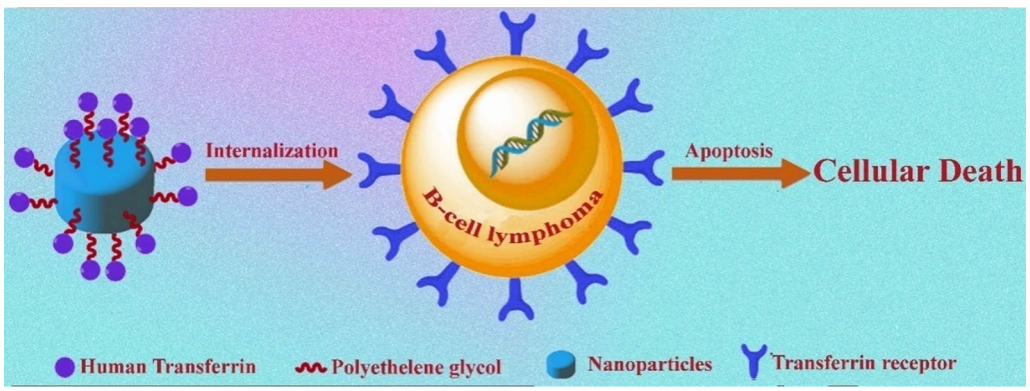


Fig. 4 NPs-based transferrin receptor targeted cancer therapy

Lectin-based targeting

Lectins are a class of proteins that has the ability to selectively recognize and attach to the carbohydrate components found on glycoproteins located on the outer surface of the plasma membrane. The glycoproteins produced on cancer cells have distinct characteristics compared to those found on normal cells. Hence, lectins have the potential to serve as targeting agents for the precise delivery of pharmaceutical compounds to specified sites [105].

Yin et al. explored lectin-conjugated PLGA NPs in 2006, loading them with thymopentin (TP5) for oral administration [106]. They did this by encapsulating the TP5 in a wheat germ agglutinin (WGA)-conjugated PLGA NP that was soluble in water. According to the TP5 in vitro release profiles, WGA-conjugated NPs release TP5 at a greater rate than non-conjugated NPs, which may be a result of WGA's hydrophilic properties. WGA-TP5-NPs exhibit improved oral absorption than conventional TP5-NPs and TP5 solution, according to in vivo pharmacodynamic tests employing FAC Scan flow cytometry on immune-suppressed rats. The higher WGA content on NPs was the cause of the improved absorption. The WGA's material in NPs has a significant impact on both the oral absorption of TP5 and the dissolution of TP5 from NPs [106]. In a different work, Mo et al. created a new isopropyl myristate (IPM) with PLGA NPs that was lectin-conjugated to enhance the anticancer activity of PTX [105]. These NPs outperformed Tx-loaded NPs with only IPM or WGA or Tx-loaded NPs with both IPM and WGA in terms of in vitro cytotoxicity against adenocarcinomic human alveolar basal epithelial cells (AS-49) and human non-small cell lung carcinoma cell line (H1299). The enhanced efficacy of these NPs in inducing cell death can be attributed to their superior cellular absorption via WGA receptor-driven endocytosis and the facilitated release of TX by IPM from the nanoparticles [105]. Targeted systems based on lectins provide several benefits. For instance, conjugating lectin to the surface of NCs can combine the cytoadhesive qualities of the lectin with the protective effects of the nanocarrier, perhaps improving the formulation's bioavailability [107].

Drug delivery using liposomes

Liposomes offer a potentially effective way to reduce the toxicity problems associated with chemotherapeutic medications since they are flexible delivery platforms for different drug encapsulation. Franco et al. conducted a study on mice with 4T1 breast tumour to investigate the impact of eliminating pharmacokinetic interaction among PTX and both DXR and its metabolite, doxorubicinol [108]. The researchers found that co-encapsulating PTX and DOX in liposomes at a ratio of 1:10 was effective in reducing the cardiac toxicity profile. An additional investigation demonstrated a technique to enhance the stability of ratiometric drug administration through the encapsulation of drug-loaded liposomes within a thermogel matrix [109]. Additionally, a persistent local release was seen in the nanohybrid carriers. The phenomenon could potentially be elucidated by the utilization of the diffusion-controlled mechanism, wherein the initial release of the embedded anthracycline from the liposomes is followed by its subsequent diffusion across the hydrogel matrix. According to in vivo experiments, the liposome-hydrogel hybrid delivery technology demonstrated lower cardiotoxicity levels than liposomal anthracycline that was not encapsulated in gel [110]. The slowly increasing data suggests that liposomal drug delivery methods can aid in the defeat of multidrug resistance (MDR). Through surface modification with dequalinium (DQ), a cationic compound that facilitates the utilization of negative mitochondrial membrane potential, Liu et al. created mitochondrial targeting liposomes. EPR and quinine (QN), two different medications, were co-loaded in the liposomes [111]. Liposomes that remained intact were taken up by mitochondria through the assistance of DQ. Subsequently, QN and EPR augmented the expression of the pro-apoptotic protein Bax and reduced the expression of Mcl-1 (antiapoptotic protein). This caused the cytochrome complex to be released and caspases -3 and -9 to be activated, which in turn caused a series of apoptotic responses in cancer cells. Using tailored liposome formulations, this work reduced the cellular impact of both extrinsic and intrinsic drug resistance. Prior to clinical rollover, stricter and more thorough review methods are needed due to the utilisation of numerous medicines in a single liposome delivery system. In particular, P-glycoprotein (P-gp) that forms efflux pumps is accountable for MDR [112]. Using a liposome platform and an intriguing nuclear-targeting approach that included the aptamer AS1411 (single stranded DNA) and DOX, it was possible to reduce MDR in breast cancer. Upon internalization by the cell, the aptamer-doxorubicin complex dissociated from the liposomes and translocated to the nucleus through an interaction between the aptamer and nucleolin. This nuclear targeting interaction made it possible for P-gp pumps to avoid the effects of DOX efflux and the treatment effectiveness was improved (Fig. 5) [113, 114].

Carbon dots-based-cancer targeting

In addition to having great optical qualities, low toxicity, strong chemical stability, a wealth of surface groups, and favourable biocompatibility [113–115], carbon dots (CDs) had been described

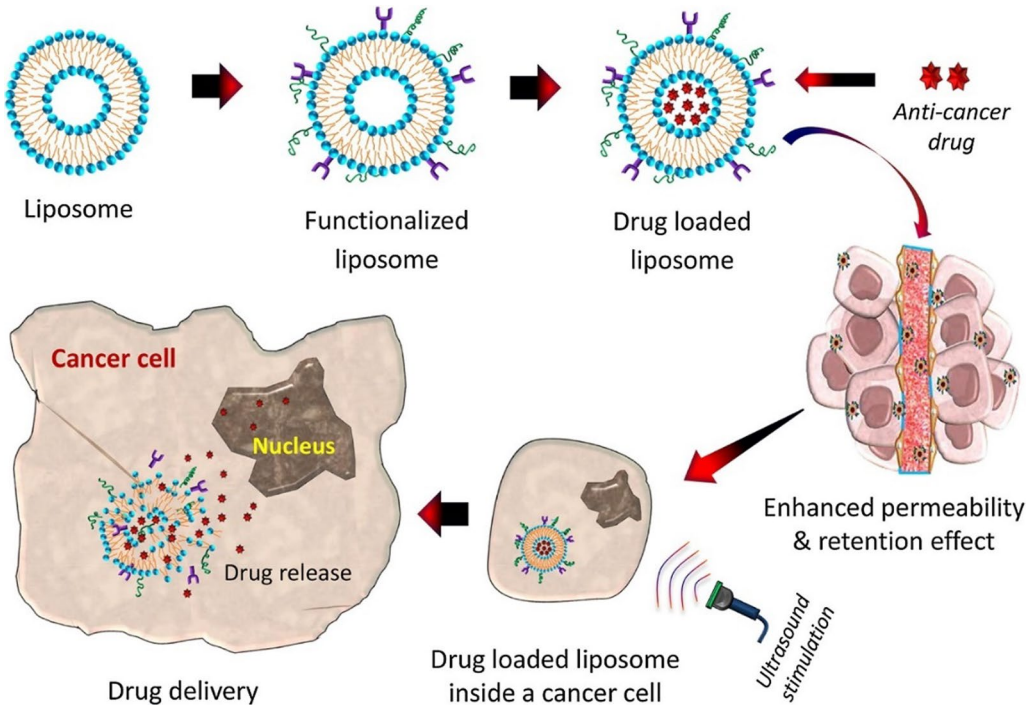


Fig. 5 Liposome-based targeted drug delivery to cancer cells (reused with permission from Hossen et al., 2019) [168]

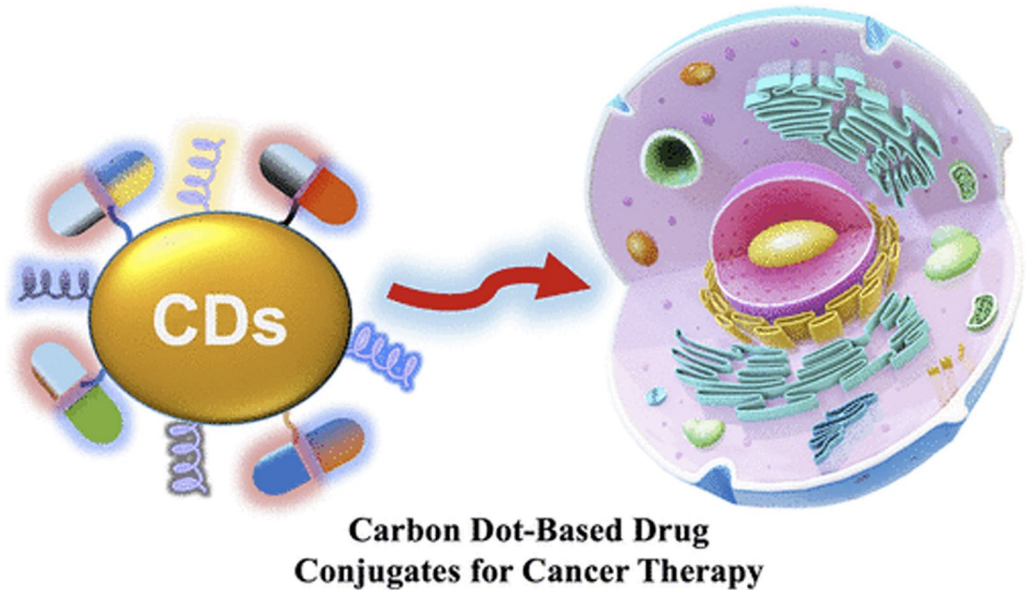


Fig. 6 Carbon dots-based cancer targeting therapy (adopted with permission from Dubey et al., 2023) [169]

as fluorescent indicators that exhibit to be suitable contenders for medicine administration. As per the recent publications, several technologies were used to synthesise CDs using different methodologies, including electrochemistry [116], teflon hydrothermal reactors [117], and microwave methods [118–120]. Several functional reagents must be coupled in order to reach the CDs' surface, including targeted ligands and anticancer medicines, in order to perform various activities. Recently, it was revealed that CDs were chemically conjugated with nuclear localization signal peptide (NLS) as a target ligand. The A549 tumour in

mice may be successfully stopped in its tracks by the complex NLS-CDs that were produced by delivering DOX to the cancer cell nucleus [121]. Compared to free DOX, demonstrated a better rate of cancer cell eradication and lower toxicity to normal cells. FA has been utilized as a navigational agent owing to the proclivity of numerous cancerous cells to exhibit elevated expression of folate receptors (FR). Current studies have shown that certain CDs have inherent tumour-targeting properties and may be employed directly as anticancer medication carriers (Fig. 6) [122, 123]. It motivated us to come up with a straightforward plan for creating new nano-drugs that can target tumours.

High-efficiency dendrimer-based NCs for anticancer medicines against cancer cells

Various dendrimers-based NCs have been used to carry a variety of drugs for high therapeutic efficacy in cancer treatment. With a predefined molecular weight, compactness, spherical 3D structures with surfaces that could be improved by attaching various drugs, hydrophobic or hydrophillic groups and size, dendrimers are a novel family of hyper-branched polymers which shows a significant interest in nano-biomedicine, such as drug delivery, gene therapy, disease diagnostics, etc. [125]. Tran et al., have discussed the preparation of generation 3.0 and 2.5 carboxylatedpolyamidoamine (PAMAM) dendrimers for loading anticancer therapy. The loading capacity of carboxylated dendrimer for cisplatin is 26.64 w/w% and dimension of the nanocomplexes ranges from 10 to 30 nm. The IC_{50} value was found to be 23.11–2.08 µg/mL with NCI-H460 lung cancer cell line. Low-diameter pegylated PAMAM dendrimers have been synthesized to deliver the 5-fluorouracil (5-Fu). The drug-loading efficiency of pegylated dendrimer was found to be satisfactory and it exhibited a delayed release profile for 5-Fu encapsulation. The nano-carrier system shows excellent potency and selectivity towards MCF-7 cell lines with IC_{50} value 9.92 to 0.19 µg/mL. The aforementioned findings demonstrate the efficacy of utilizing dendrimer nanocarriers for the purpose of delivering medications in the treatment of cancer [125].

Colon cancer prevention

The most prevalent cancers include colon cancer. Surgery is frequently used as the initial treatment for patients with localised colon cancer, and chemotherapy regimens are frequently given for around 6 months after surgery, albeit their efficacy is still restricted [125]. CD98, a transmembrane glycoprotein, has been identified as a distinguishing feature of colon cancer cell apical membranes. Its expression has been found to be elevated and it is considered a potential pharmacological target for the transportation of drugs to colon malignancies. Xiao et al. have developed a treatment strategy for colon cancer that involves the use of CD98-siRNA and camptothecin-loaded PEGylated Fab-NPs, which are embedded in a hydrogel [26]. The aim of this approach was to target a specific receptor. Due to increased drug internalisation into the tumour cells than in NPs containing a single drug, the dual system therapeutics efficacy has been established by using mouse models of orthotropic colon tumours [126]. Numerous miRNAs exhibit in-vitro anti-colon cancer activity, but there in-vivo uses are limited due to biofluid breakdown and insufficient cellular absorption. MiR204-5p is markedly down-regulated in colorectal cancer cells as compared to healthy cells. Zheng and colleagues employed a surface functionalization method to fabricate poly(D,L-lactide-co-glycolide)/poly(L-lactide). Block-poly(ethyleneglycol)-folate polymer nanoparticles with miR-204-5p added on them which show anticancer efficacy that effects on in-vivo colon tumour xenograft models and colon cancer cells [32]. In this study, the NP system was shown to be a cutting-edge technique for delivering miRNA to *in-vivo* colon cancer cells. Galectins, which are proteins that exhibit binding affinity towards galactosides, have been found to be upregulated in cases of colorectal cancer. These proteins are recognized to have a pivotal function in modulating the progression, metastasis, and dissemination of the disease.

Liu et al., have developed galectin-recognition materials using galactosylated chitosans based on mesoporous silica NP for colon cancer. The inorganic–organic nanocomposite exhibited higher efficacy in terms of loading capability, discharge duration, and cytotoxic effects towards human colon cancer cells in comparison to unbound 5-Fu [43]. Jiang et al. have synthesized 5-Fu loaded mesoporous silica nanoparticles and examined their impact on colon cancer cells [127]. The CD44 receptors, which are over-expressed in cancerous cells, were identified as the target of HA on the surface of nanoparticles. The process involves the selective attachment of biotin-to-biotin receptors that are over-expressed upon the surfaces of colon cancer cells. Lin and colleagues synthesized silica nanoparticles loaded with doxorubicin and modified with polyethylene glycol and biotin. Their findings demonstrate effective anticancer activity against HCT116 cells and tumour-bearing mice [128]. In other way, silymarin (SLM), which had previously been restricted as an anticancer medication due to its poor bioavailability. Recently, SLM can be nanostructured and encapsulated in micelles which prevented the growth of colon cancer cells and

raised their apoptotic and necrotic indices while having no effect on healthy colon cells [129]. As we know, curcumin (CUR)has well anticancer properties but their utility is limited due to poor absorption, rapid metabolism, and subsequent oxidation. Alkhader et al., reported encapsulating CUR in a chitosan (CS)-pectinate (PEC)-NP system (CUR-CS-PEC-NPs) to increase its capability to target the colon cancer [130]. Pectin is one of the most common carriers for CUR. The results indicate that CUR-CS-PEC-NPs possess promising attributes for oral delivery in the context of colon cancer therapy, and offer a foundation for the design of carriers with analogous structural characteristics to enhance the tumour-specific delivery of natural anticancer agents. To improve the anticancer efficacy of CUR against colon cancer, pH-responsive xylan-CUR prodrugs were developed in a distinct experiment. The synthesized NPs exhibit pH-responsive behaviour, allowing for the release of their drug payload under acidic conditions. The enhanced potency of these NPs towards human colon cancer cells, in comparison to the pure drug, can be attributed to this pH responsiveness [131]. New redox-sensitive prodrug NPs containing xylan-SS-CUR have been described in recent research for the administration of curcumin and 5-Fu against human colorectal cancer cells. The utilization of novel NPs has demonstrated potential as a drug delivery system for enhanced cancer treatment by augmenting the anticancer activity of the loaded drugs [132]. In a separate study, conjugates of xylan-5-Fu-1-acetic acid were reported for the target specific treatment of colon cancer. Results demonstrated that the drug's capacity to cure human colon cancer was enhanced by polymeric conjugates [133]. The study revealed that the administration of amphiphilic xylan-stearic acid-based NPs resulted in enhanced anticancer efficacy of 5-Fu against human colon cancer cells [134]. Olchicine is an alkaloid prodrug that occurs naturally and functions as an anti-mitotic agent for the treatment of cancer. Nonetheless, its efficacy against cancer is limited due to its significant cytotoxicity. A recent study has documented the utilization of mesoporous silica NPs that have undergone functionalization with phosphonate groups and embellishment with a chitosan-glycine complex that contains FA. The purpose of this approach is to facilitate the distribution of colchicine [135]. It was suggested that the colchicine-laden NPs increased anticancer and antimitotic activity. Another experiment stated that EGF functionalized PLGA NPs were used to deliver 5-Fu and perfluorocarbon for the efficient treatment of colon cancer.By targeting certain receptor, the functionalized NPs were able to prevent tumour development [136].

Cervical cancer prevention

The fourth most common malignancy in women and representing 3% of new cancer cases is cervical cancer [137]. In several studies show that NPs have good potency and selectivity towards various cervical cancer therapy. As per literature, the silver NPs can exhibit antibacterial, anticancer, and anti-inflammatory properties. Al-Sheddi et al. have prepared silver NP by using aqueous Nepeta-deflersiana plant extracts and reported anticancer properties against HeLa cell line. The above NPs can initiate lipid peroxidation, produce ROS, and finally cell cycle arrest at subG$_1$ phase [138].

Yuan et al., have reported silver NPs and camptothecin, a topoisomerase inhibitor for their potential synergistic effects on HeLa cells [28, 139]. The activation of caspases 9, 6, and 3 and changes to the permeability of the mitochondrial membrane made this combination effective in the treatment of cervical cancer. The combination of NPs and drugs represent a possible strategy in study of cancer. Luo and colleagues created polylactic-co-glycolic acid NPs which is modified by biotin, and showed reducing intracellular ROS formation, and enhance the impact on proliferation of 15,16-dihydrotanshinone I in HeLa cells [44, 140]. Due to the over-expression of the transferrin receptor in cancerous cells relative to healthy cells, transferrin was extensively utilized as a chemical agent for targeting cells. Boondireke et al., have used monoacylglycerol monomyristin (encapsulation) from the saw palmetto palm, in dextran-coated polylactide NPs linked to transferrin and showed increased cytotoxicity profile of monomyristin in HeLa cells. Anticancer properties and water solubility efficiency of monomyristin were enhanced via encapsulation of NPs and targeting transferrin receptor [141]. In other way, cisplatin (CDDP), first metal-based drug for cancer treatment but its usage has been constrained because it is not selective for cervical cancer treatment. As a result, Cheng et al., implemented CDDP by using fluorescein PEG amine grafted-aldehyde HA (Cy5.5- PEG-g-A-HA) NPs and increase acidic pH response for cervical cancer [142]. While HA is an agent that targets in NCs, a significant portion may collect in the liver and could be quickly excreted. This problem appears to have been lessened and aldehyde HA (A-HA) was used in this experiment. The results showed that CDDP was well-tolerated by the body and NPs can effectively target cervical tumours and trigger apoptosis. In another report, preparation of lipid polymer NPs and surface modified by folic acid to treat cervical cancer with pH-sensitive tailored administration of carboplatin and paclitaxel. The dual-functionalized NPs were able to suppress tumour growth by targeting specific receptor and pH-responsive drug release in

cervical cancer cells [143]. Furthermore, the synthesis of layer-by-layer (multifunctional) mesoporous calcium carbonate nanoparticles with regulated drug release properties for the targeted delivery of doxorubicin to cervical cancer cells. The creation of intelligent nanoparticles has been achieved through a layer-by-layer approach, utilizing folic acid as a ligand for targeting cancer cells, and replacing components with sodium alginate and chitosan. Transfection of cervical cancer cells with doxorubicin was regulated by using pH responsiveness and receptor recognition [144]. An innovative bioinspired NP method for administration of siRNA and paclitaxel for the successful treatment of cervical cancers was revealed in recent research. A novel biomimetic approach was employed to develop a dual-drug delivery system, wherein siRNA and paclitaxel were encapsulated within PLGA nanoparticles coated with HeLa cell membrane. The newly developed biomimetic dual-drug delivery system demonstrated an enhanced ability to achieve drug-specific tumour localization through its immune escape capability. Therefore, the cervical tumour volume was reduced by about 83% without causing adverse effects to the major organs [145].

Breast cancer

The second most prevalent kind of cancer is breast cancer (BCa) [146]. However, photothermal treatment (PTT) is viewed as a desirable anticancer treatment, cancer cells treated with PTT may become thermoresistant which is attributed to the over-expression of heat shock proteins (HSPs), notably heat shock protein 70 (HSP70). Hence, preventing increased HSP70 may reduce the tumour cells resistance to PTT. In addition to inhibiting HSP70, protein kinase B and caspase-3 are likewise inhibited by the dietary flavonoid quercetin. As opposed to that, NPs are given significant benefits by a cell membrane-camouflaged mechanism.

A novel therapy for breast cancer was developed by Zhao et al. in which hollow bismuth selenide nanoparticles loaded with quercetin (M@BS-QE NPs) were disguised with macrophage membranes [30, 147]. Due to the M@BS-QE NPs ability to evade the immune system, they were able to remain in the bloodstream for longer periods of time, which increased the accumulation of BCa cancer treatment. Quercetin increased active targeting, made cancer cells more responsive to photo-therapy, and inhibition of tumour development and metastasis when combined with bismuth-based NPs and macrophage membranes. Tumour metastasis and actin cytoskeletal remodelling have a strong relationship. Qin et al., have developed novel small-sized fullerenol NPs which affect migrating BCa cells. The NPs might interfere with the dynamics and rearrangement of the actin cytoskeleton in cancer cells and prevented the aggressive BCa from spreading [148]. Piceatannol, a polyphenol was synthesised by Dhanapal and Balaraman Ravindran coated with PLA and chitosan NCs for anticancer therapy [37, 149]. Combining chitosan with the PLA polymer prevented chitosan from degrading. By continuously releasing the encapsulated piceatannol, these polymeric NPs increased the effectiveness of cytotoxicity through mitochondria-dependent mechanisms of BCa and other neoplastic cell lines. In combination with photothermal treatment, Kong et al. have devised (DTX-) loaded cholic acid-functionalized AS1411 aptamer-polydopamine-poly(caprolactone-ran-lactide) (CA(PCL-ran-PLA)), which reduced the risk of BCa development [150].These NPs look potential for the synergistic chemophotothermal method of BCa because of their great biocompatibility and few negative effects. Metformin, a biguanide anti-diabetic drug has shown to increase the susceptibility of BCa cells with Dox resistance through reducing activity of P-gp, according to Shafiei-Irannejad et al., [151]. They have reported Dox and metformin-encapsulated biodegradable PEG 1000 succinate NPs containing poly(lactide-co-glycolide)-D-tocopheryl, which were effective in inactivating resistant BCa cells [152]. It may be useful to delivery metformin and Dox using polymeric NPs.

The most widely used MOF is Zeolitic imidazolate Framework (ZIF-8), pH-responsive for drug release which is utilised because it is more porous, sensitive, and capable of holding more drugs. Tian et al., developed fluorescein-ZIF-8/graphene oxide nanocrystals with acidic pH-responsive fluorescein release [153]. Due to the photothermal impact 4T1 breast cancer cells were effectively inactivated. Chen et al., developed ATP-responsive Dox-loaded aptamer-gated nano-MOFs and used in MDA-MB-231 BCa cells, the results reveal that around 40–55% cells are died after 5 days of treatment [154]. Moreover, they have reported on a Zr-MOF which is Dox-loaded, ATP/Mg^{2+} sensitive and selectively lethal to MDA-MB-231 cell lines [155]. The nucleolin receptor sites are the target of the aptamer because cancer cells overexpress ATP, which results in increased nano-MOF cell penetration.

In order to effectively distribute doxorubicin for breast cancer treatment, multiwalled carbon nanotubes have been coated with glycopolymers conjugated with folic acid, according to a recent study. By simultaneously targeting the folic acid receptors and the glucose transporter protein in breast cancer cells, doxorubicin was administered to breast cancer cells with precision [156]. Another recent study described the use of gold NPs with folic acid-functionalized surfaces for breast

cancer treatment with a combination of chemotherapy (methotrexate) and phototherapy. Due to the specific distribution and overexpression of folic acid receptors on the surfaces of breast cancer cells, the nano technology enhanced the effects of combined chemo-phototherapy [157]. The selective administration of paclitaxel using dual targeting polymeric NPs for the treatment of bone metastatic breast cancer was also described. To achieve dual drug targeting, alendronate-modified D-tocopheryl polyethylene glycol succinate and folic acid were used to adorn the NPs. The innovative approach demonstrated hydroxyapatite binding affinity and subsequent receptor-mediated internalisation, demonstrating superior therapeutic outcomes for the medication in the context of bone metastatic cancer by reducing tumour incidence and elevating rate of survival [158].

Lung cancer

According to an ACS assessment from 2012, lung cancer causes 335,000 deaths per year in Europe and 160,000 in the USA. Furthermore, 85% of the cases mentioned are non-small cell lung cancer (NSCLC). In Spain, both the overall incidence and recurrence of lung cancer among males have grown during the past century. Lung cancer is still more common in males, but as smoking patterns change, it is also becoming more common in women [159–161]. The transmembrane protein EGFR, sometimes referred to as the EGF receptor is involved in essential growth factor signalling from the extracellular environment to the cell [162]. Since, EGFR has emerged as a key target for cancer therapy, since it accounts for more than 60% of NSCLCs [163, 164]. The usefulness of using nanotechnology in drug administration has considerably expanded with the development of several nanoparticulate systems, such as liposomes, NPs, and other nanoparticulate systems. The traditional NCs have certain drawbacks, such as drug leakage and stability problems. These problems have been overcome utilising strategies such as covering the NPs and employing stimuli-responsive NCs. Additionally, these techniques support the achievement of organ-restricted drug delivery and enhancement of pre-existing properties. These kinds of smart NCs have found to use in fighting cancer because cancer tissues have a specific pH and enhanced enzyme levels. The effectiveness of several NCs carrying diverse compounds against lung cancer has also been developed and evaluated. They have reported various kinds of stimuli-responsive NCs, as well as exogenous stimuli-responsive NCs such asthermos-responsive, magnetic-responsive, ultrasound-responsive, and photo-responsive NCs and their use to targeting lung cancer [165].

Skin cancer

Skin cancer, one of the most prevalent and challenging kinds of cancer, has one of the highest global mortality rates. Chemotherapy, surgery, radiation, and other therapies are currently offered for skin cancer. The kind of skin cancer and the patient's health are often taken into consideration when choosing a treatment plan for skin cancer. The therapeutic efficacy of skin cancer treatment remains restricted owing to inadequate drug penetration into the lesions or stratum corneum, suboptimal effectiveness, and the necessity for elevated concentrations of the pharmacologically active constituents to elicit a therapeutic response. Additionally, the need for high doses, low bioavailability at the site of action, and drug absorption through the stratum corneum is considerably hindered by skin irritation. In order to circumvent the problems with conventional anticancer pharmaceutical delivery methods, NCs have been developed. The present state of skin cancer treatment has showed significant promise for nanotechnology-based therapy, and these could potentially serve as a more effective method for delivering drugs to treat cancer. Researchers have also looked at the several nanoparticulate therapy modalities and how well they treat skin cancer [166].

Hepatic cancer

Extracellular matrix (ECM) and cancer associated fibroblasts (CAF) have been identified as major actors in biology of cancer and have become crucial cancer-related targets therapy and medication development. Both the specific ECM and CAF components are detected in tumours that lack a noticeable desmoplastic reaction within the tumour, as well as in tumours that are rich in stroma, such as pancreatic, biliary, and certain sub types of hepatocellular carcinoma (HCC). Cancer is supported by various mechanisms such as extracellular matrix remodeling, angiogenesis, and active immune-suppression. These mechanisms involve the secretion of tumour-promoting and immune-suppressive cytokines, growth factors, and chemokines. They contribute to the developing, growing, metastasis, and resistance of cancer to chemotherapy or checkpoint inhibitor therapy. Cancer-associated fibroblasts (CAFs) exhibit similarities to activated hepatic stellate cells (HSC)/myofibroblasts due to their expression of smooth muscle actin and fibroblast activation protein (FAP). CAFs have been observed to upregulate additional functional cell surface proteins, such as the insulin-like growth factor receptor II (IGFR II) and platelet-derived growth factor receptor (PDGFR). Notably, NPs were injected preferentially to

Table 1 NCs in cancer medication delivery (reused from Kaushik et al., 2022, distributed under Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium. (http://creativecommons.org/licenses/by/4.0/) [170]

NC	NC@drug	Material advantage	Specificity	References
Liposomes	Liposomal doxorubicin	Improved delivery to site of disease; decrease in systemic toxicity of free drug	Ovarian cancer; multiple myeloma	[172]
	Liposomal daunorubicin	Improved delivery to tumour site; lower systemic toxicity arising from side effects	Karposi's sarcoma	[173]
	Genistein and plumbagin encapsulated nanoliposomes	Inhibition of cell metabolism	In vitro and in vivo prostate cancer	[174]
	Folate-conjugated bovine serum albumin bound paclitaxel NPs	Increased solubility, cellular uptake; targeted specificity	Prostate cancer cells	[175]
Protein-based NPs	Alpha mangostin loaded crosslinked silk fibroin-based NPs	Physico-chemically stable, increased the drug's solubility	Colorectal and breast cancer	[176]
	Noscapine-loaded human serum albumin NPs	High drug-loading efficiency (85–96%) and delivery of maximum quantity of drug to the tumour site	Breast cancer cells	[177]
	Plasmid cDNA (pGL3) polyethyleneimine (PEI)-coated HSA NPs	Enhance endosomal escape	In vitro gene delivery application	[178]
Micelles	Polymeric methoxy-PEG-poly(D,L-lactide) micelle formulation of paclitaxel	Improved delivery to site of disease; decrease in systemic toxicity of free drug	Breast cancer; ovarian cancer	[179]
	Folate-PEG/Hyd-curcumin/C18-g-polysuccinimide	pH sensitive drug release	Colon cancer	[180]
	PEGylated prodrug nano-micelles	Glucose-sensitive	In vitro and in vivo anticancer activity	[181]
Polymeric Micelles	CD44v6-targeted polymeric micelles (PM) loaded with niclosmide	Increase drug safety	Efficacy against colorectal stem cells	[182]
Self-assembly	Aptamer-tethered DNA assembly	Stronger targeting ability, higher cellular uptake	Cancer cell imaging	[183]
	DNA-aptamer conjugated RNA-triple helix hydrogel	Efficient cellular uptake and enhanced nuclease resistance with superior biocompatibility	Triple negative breast cancer detection and treatment	[184]
	Folate-modified MPEG-PCL	Improved bioavailability, low toxicity, sustained drug release	Colorectal cancer mice model	[185]
	Folate receptor-targeted β-cyclodextrin (β-CD)	Biosafety, bioavailability, and improve curcumin drug loading capacity	Cervical cancer, fibroblast cells	[186]

Table 2 A compilation of the NCs employed in clinical trials (reused from Kaushik et al., 2022, distributed under Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium. http://creativecommons.org/licenses/by/4.0/) [170]

Products	Drug	Nanocarrier	Application
Lipoplatin	Cisplatin	Liposomal	Non-small cell lung cancer
Onco-TCS	Vincristine		Relapsed non-Hodgkin lymphoma
OSI-211	Lurotecan		Head, neck, and ovarian cancer
SPI-077	Cisplatin		Head, lung, and neck cancer
PNU166945	Paclitaxel	Polymeric	Solid tumours
XMT-1001	Camptothecin		Gastric cancer and lung cancer
PEG-SN38	Irinotecan derivate		Solid tumours and breast cancer
Livatag	Doxorubicin		Liver cancer
NKTR-105	Docetaxel		Solid tumours and ovarian cancer
Paclical	Paclitaxel		Breast, lung, and ovarian cancer
PEG-docetaxel	Docetaxel		Solid tumours

the liver if they are designed with an appropriate size and zeta potential. A variety of formulations tailored to nanotechnology were successfully used to assess the delivery of drugs to activated HSC/myofibroblasts. The surface modification of nanoparticles with cyclic peptides that bind to the PDGFR or mannose-6-phosphate that binds to the IGFR II has proven to be effective in directing the delivery of drugs to stimulated HSC/CAF in vivo. Lipoplexes and unguided nanohydrogel particles containing siRNA have exhibited a significant in vivo uptake and functional delivery of siRNA in activated HSCs. This is attributed to the specific targeting of liver CAFs and HSCs by well-designed NCs with optimized physico-chemical characteristics. As a result, CAFs have emerged as a highly desirable target for stroma-focused cancer treatments, with a particular emphasis on liver cancer [167].

Tables 1 and 2 demonstrated the NCs employed in cancer medication delivery and the NCs under clinical trial, respectively [187–195].

Conclusion and prospects for the future

Chemotherapy for various cancers is recommended due to its less intrusive nature. Some chemotherapeutic medicines lack target specificity and physicochemical characteristics, limiting their clinical application. This lowered efficacy and caused major negative effects. The aberrant biology of the cancer microenvironment complicates drug targeting. NCs are interesting cancer therapeutic targets due to their small size and changed physicochemical properties.The attractive surface characteristics of certain NCs also influenced its selection. Researchers in cancer research prefer NCs with surface-engineered payload release at the tumour location. Drug researchers are working hard to create NC-based targeted delivery systems for breast, colon, ovarian, and lung cancer. The research suggests that lipid, liposomes, polymeric, metal nanoparticles, micelles, carbon nanotubes, and nano-MOFs may deliver chemotherapeutic medications to particular cancer sites for cervical, colon, lung, and breast cancer. Surface-functionalized NCs with enhanced redox status, acidic pH, or hypoxia-responsive NPs may target cervix, breast, colon, and lung cancers. The bulk of the currently authorised nano-drugs come from straightforward NPs and recognised conventional drugs.

Failure of NPs in late-stage clinical trials is often attributable to their disease heterogeneity, chemical, physical, and biological instabilities, and unanticipated in vivo behaviour. These factors also contribute to the absence of recognised procedures for assessing the toxicity of NCs and nanodrugs. Preventing NPs from failing in clinical trials and permitting effective regulation of their stability, biocompatibility, and consistent in vivo behaviour need an understanding of the heterogeneity of cancer and the fundamental properties of NPs. Similar to this, research in nanomedicine for treating breast, colon, ovarian, and lung cancer has been dominated by early-stage formulation and material investigations. It is recommended to employ multidisciplinary methods and just animal experiments to acquire information about possible medicinal applications. The prospect for NCs technology's multifaceted future seems bright, given the worldwide trend towards precision medicine. Moreover, regularity procedures continue to be a key barrier; as a result, a simple and comprehensive approval procedure method should be developed. Nonetheless, nanodrug platforms are growing increasingly sophisticated and include a wide variety of NP types. Future clinical usage of various novel nanodrugs is predicted by the research being done in this field. Additionally, current research in this area indicates that intelligent NP systems will soon be able to diagnose illnesses, monitor patients' health, and deliver targeted chemotherapy all at once. Although there are numerous obstacles to overcome in the creation of nanodrugs, it could only be a matter of time until these substances provide distinctive remedies for unmet therapeutic requirements.

Abbreviations

A549	Human lung cancer cell line
AS-49	Adenocarcinomic human alveolar basal epithelial cell
BCa	Breast cancer
CAF	Cancer associated fibroblasts
CD	Carbon dot
CD44	Cell surface adhesion receptor
CS	Chitosan
CUR	Curcumin
CXCR4	Chemokine receptor
DDS	Drug delivery system
DQ	Dequalinium
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGCG	Epigallocatechin-3-O-gallate
EPR	Enhanced permeability and retention effect
FA	Folic acid
FDA	Food and drug administration
FAP	Fibroblast activation protein
FR	Folate receptor
HA	Hyaluronic acid
HSC	Hepatic stellate cell
HSP	Heat shock protein
HuR	Human antigen R
H1299	Human non-small cell lung carcinoma cell line
IF	Intrinsic factor
IGFRII	Insulin-like growth factor receptor II
IPM	Isopropyl myristate
LCa	Lung cancer
MCF-7	Human breast cancer cell line
MDA-MB-231	Human breast cancer cell line
MDR	Multidrug resistance
MOF	Metal–organic framework
MNC	Micellar nanocomplex

NC	Nanocarrier
NLS	Nuclear localization signal peptide
NP	Nanoparticle
NSCLC	Non-small cell lung cancer
PAMAM	Polyamidoamine
PDGFR	Platelet-derived growth factor receptor
PEC	Pectinate
P-gp	P-glycoprotein
Pt	Platinum
PTT	Photothermal treatment
PTX	Paclitaxel
QN	Quinine
RM	Reverse micelle
ROS	Reactive oxygen species
SLN	Solid lipid nanoparticle
TcII	Transcobalamin II
TSL	Thermosensitive liposomal formulation
TP5	Thymopentin
VB12	Vitamin B12
WGA	Wheat germ agglutinin
5-Fu	5-Fluorouracil

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Author details
[1]Kolkata – Group of Institutions, NSHM Knowledge Campus, 124, B.L Saha Road, Kolkata 700053, India. [2]Department of Pharmaceutical Chemistry, Gupta College of Technological Sciences, Asansol, West Bengal 713301, India. [3]School of Pharmacy, Sister Nivedita University, DG 1/2 New Town, Action Area I, Kolkata 700156, India. [4]Department of Pharmaceutical Technology, Brainware University, Barasat, Kolkata, West Bengal 700125, India. [5]Department of Chemistry, School of Advanced Sciences, Vellore Institute of Technology, Vellore, Tamil Nadu 632014, India. [6]Department of Pharmaceutical Technology, Eminent College of Pharmaceutical Technology, Barasat, Kolkata 700126, India.

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