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Review article

Role of nanoparticles in enhancing chemotherapy efficacy for cancer treatment

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ABSTRACT

This article is an overview of the current state of nanoparticles because of their emerging usage in cancer treatment, covering nanoparticles that have been authorized for use in cancer therapy currently undergoing clinical testing. Recent advances in nanoparticle engineering, coupled with an enhanced understanding of critical nanoparticle attributes (size, shape, and surface properties) in conjunction with biological systems, present novel prospects for therapeutic nanoparticle development. Although inorganic and metallic nanoparticles are gaining recognition in clinical studies due to their potential usefulness but nanomaterials primarily polymeric, liposomal, and nano crystal based dominate the cancer therapy. Polymeric nanoparticles (NPs) contain specific ligands, such as polyglycolic acid (PGA) and polylactic acid (PLA), which have a chemical affinity for malignant cells and target tumors. Nanocrystals stand out with their high loading efficiency, stability, extended drug release, and capacity to deliver poorly soluble medications. The limitations of conventional chemotherapy are overcome in a variety of applications for improved cancer care by metal-based nanoparticles, either used alone or in combination. The dynamic nature of nanotechnology drives continued developments like protein-based nanoparticles and micelles. Polymer and lipid encapsulation within nanocrystals is becoming more and more popular, suggesting a long-term trend. This advancement marks a significant breakthrough in life-saving nanotechnology, particularly in cancer treatment, and sets the stage for pioneering applications in nanomedicine.

1. Introduction

The most crucial obstacle to extending the average lifespan in the twenty-first century is cancer, currently the leading cause of mortality worldwide. Genetic and epigenetic factors may influence tumor growth and recurrence. The prevalence of cancer is rising in emerging nations due to factors like population aging and development, as well as controllable elements like smoking, sedentary behavior, and modern foods [1]. Due to the complicated interaction of inherited and environmental factors, cancer is a multifaceted disorder. The defects that

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lead to cancer are primarily brought on by DNA damage [2]. According to cause-specific disability-adjusted life years (DALYs), cancer has the most significant clinical, social, and economic impact of any human disease. Chemotherapy has a crucial drawback in that it is hard to reach tumor tissues, whereas radiotherapy and immunotherapy are other traditional cancer treatments. A variety of adverse drug reactions are linked to the need for high doses and the nonselective nature of the treatment choices that are now accessible [3,4].

Nonetheless, combination treatments for the treatment of cancer are growing in popularity. These therapies merge two or more anticancer drugs to increase their anticancer effects, lessen their possible side effects, and prevent the development of drug resistance. Nanotechnologies are essential to provide effective anticancer combination medication delivery that distributes pharmaceuticals to targeted tumor tissues. Moreover, targeted and controlled drug delivery systems improve chemotherapeutic agents' safety profile while increasing therapeutic efficacy [5].

An innovative method of cancer drug delivery using nanoparticles (with sizes in the nanometer range) functions as a carrier for entry through open windows in tumor vasculature, giving direct cell access [6–8]. These particles permit acceptable customization for attaching to the microenvironment, cytoplasmic or nuclear receptor sites, or the membranes of cancer cells. As a result, the targeted cancer cell receives high medication concentrations with minor damage to healthy tissue [9]. The application of nanotechnology to medicine, or "nanomedicine," offers important tools for the detection and treatment of disease. Many submicron materials have been developed and produced in this way, especially for the treatment of cancer. The development of drugs, drug delivery methods, theranostics, and contrast agents is accelerated by applications. Biodegradable and biocompatible polymers derived from natural or synthetic materials have been utilized to create nanoparticles (NPs) for use in drug delivery applications. Synthetic polymers can be produced precisely, well-controlled, and with high degrees of purity compared to natural materials [10].

Among all the nanoparticles, metal NPs have drawn particular attraction because of their ability to function as versatile agents. Numerous metal nanoparticles (NPs) with bases in bismuth, zinc, titanium, cerium oxide, gold, silver, iron, or iron oxide, calcium, barium, magnesium, copper, and nickel have been reported as cancer therapies [11–13]. Metal NPs play a vital role in the ongoing cancer research platforms, and the area of research in this domain is steadily growing, as seen when five widely manufactured metal nanoparticles were analyzed; gold NPs came out on top, followed by magnetic and silver nanoparticles (MNPs) [14]. Drug delivery using Nanoparticles composed of gold, silver, or metal compounds has drawn much attention from researchers. One of the metal-based NPs that has been studied the most in medicine is old nanoparticles (Au NPs) [15]. Au NPs have several desirable characteristics, including minimal immunogenicity and toxicity, high stability, increased permeability and retention, intrinsic immune activation capabilities, and an easily changeable surface.

This review's main objective is to determine nanoparticle properties, tumor-destructive effects, toxicity, and possible applications in cancer treatment. Technically, particles having a single dimension of less than 100 nm are referred to as NPs, and they usually possess unique characteristics that are absent from bulk materials of the same chemical composition [15]. The core of NPs, which is essentially its central section and sometimes referred to as the NP itself, comprises of the shell layer, surface layer, and other layers [16]. These materials have grown significantly in various disciplines due to their unique qualities, including high surface-to-volume ratios, dissimilarities, sub-micron sizes, and enhanced targeting systems [17]. Moreover, NPs are classified as hybrid nNPs, combining more than one nanostructure form. Table 1 includes diagnostic and therapeutic nanocomponents [20].

Medicine, MRI contrast agents, cancer diagnostics, and catalysis have all benefited from using metal NPs [18]. These substances can be coupled with Iron Oxide nanoparticles (IONPs) that demonstrate various characteristics. Gold, silver, copper, platinum, and palladium are a few of the coatings employed. Also, these structures can be altered by varying the surface charges or functional groups of IONPs, increasing their compatibility and stability [19]. IONPs functionalized with poly (ethylenimine), and gold produced intriguing multifunctional Nano platforms for the bimodal application of light and magnetic hyperthermia while also exhibiting very low cytotoxicity employing the micro-emulsion approach to create IONPs that were aptamer and gold-functionalized to target breast cancer cells [20].

Table 1
Two principal designs for hybrid Nanoparticles.

Component	Types of Nanoparticles	Function	References
Therapeutic Nanocomponent	Liposome, polymer, and virus	Drug delivery	[20]
	Gold nanoparticles, Carbon Nanotubes	Photothermal heating	
Diagnostic Nanocomponent	Gold Nanoparticles and Nano dot	Optical imaging	
	Magnetic Nanocrystal	MRI, Magnetic Targeting	

In order to boost the effect of enhanced permeability and retention (EPR), NPs are discovered to have deep tissue penetration. Moreover, bioavailability and half-life are impacted by surface characteristics that effectively overcome epithelial fenestration [15]. To prevent particle aggregation, the polymers produce electrostatic repulsion and steric effects. The most researched coatings are made of polymers such as polylactic acid (PLA), polyvinyl alcohol (PVA), polyethylene glycol (PEG), and polymethyl methacrylate (PMMA) [16]. Moreover, researchers have developed coverings of intelligent polymers that react to many incitements, including pH, temperature, light, and others [17]. The manufacture of NPs for cancer treatment frequently uses natural polymers include starch, chitosan, dextran, and gelatin.To improve the stability, biocompatibility, and biodegradability during the manufacturing process, these chemicals function as stabilizers [18]. GEL NPs may be used as stable drug carriers for cancer treatment with two therapeutic effects (hyperthermia and chemotherapy) [19].

2. Passive targeting

Passive targeting increases EPR [21]. This can only happen if the endothelium lining the blood vessels supplying the tumor develops fenestrations. Large NPs can enter the tumor through channels and enhance its permeability effect. The retention effect occurs because the lymphatic system is compromised in tumor tissue, making it harder to recapture these macromolecules [22–27]. Due to physicochemical or pharmacological variables, this process is known as passive targeting and it occurs when a drug or drug-carrier structure is placed at a certain location [28,29]. The absence of lymphatic outflow makes NP retention easier. However, small molecule medicines do not share this property due to their rapid circulation and elimination from the tumor. Yet, there's a silver lining. Incorporating small-molecule medications into nano-sized drug carriers increases certain tumor selectivity, lessens adverse effects, and improves pharmacokinetics (longer systemic circulation). The features of the carrier (size, circulation duration) and the biology of the tumor determine the success of this' passive' tumor targeting [30,31]. This innovative approach offers a glimmer of hope for improved cancer treatment. The restricted lymphatic drainage and leaky vasculature that characterize solid tumors make NPs ideal candidates for passive targeting. The EPR was initially documented by Matsumura and Maeda in 1986. Macromolecules and NPs with molecular weights greater than 50 kDa can preferentially accumulate in the tumor interstation [32]. By changing the EPR effect, you can get more nano-carriers to gather and help blood vessels return to normal. Bradykinin, nitric

oxide, peroxynitrite, prostaglandins, chemical EPR enhancers include vascular endothelial growth factor and various cytokines [33]. These medications normalize or increase blood pressure in the vessels, which may have a short-term beneficial effect on tumor perfusion. Many methods, such as ultrasound, radiation, heat, and photo-immunotherapy, can change the tumor's vasculature and increase nano-systems permeation [34–37].

Despite the vast and phenotypic diversity of cancerous cells and tumors, only a few methods exist for focusing on malignancies cancerous cells have gained widespread application. The EPR effect, however, stands out. It enables the passive targeting of anti-tumor medications for various cancers, some vascularized solid tumors, and a few vascularized metastatic tumor masses [38]. Certain situations (inflammation/hypoxia, typical of cancers) cause the blood vessel endothelium to become more permeable than it is in a healthy state [39]. The diversity in EPR effects within and between different cancers can impact the therapeutic efficacy of passively targeted NPs. This versatility of the EPR effect, where the endothelial gap might range from 1 to 100 nm and the varied extravasations of NPs into the tumor, is genuinely admirable [40]. Despite some research suggesting that NPs delivered intravenously are more likely to extravagate to the tumor's periphery, NPS may be more likely to extravagate into the tumor's hypoxic center than into the tumor's more permeable peripheral [41,42]. Fig. 1 provides a schematic representation of active targeting and passive targeting tumors, further illustrating the remarkable adaptability of the EPR effect.

2.1. Case study: architectural abnormalities of the neoplastic vessels and blood pressure

The smooth muscle layer in healthy blood arteries is crucial for regulating the vasogenic reaction to mediators in the vascular system and, as a result, ensuring that an organ receives steady blood flow. On the other hand, the microvasculature in neoplastic tissues is devoid of these smooth muscle cells; as a result, these vessels are permanently vasodilated and unresponsive to physiological stimuli that control blood flow. The irregular fluid and solute transport dynamics caused by these aberrant neoplastic channels across tumor vessels can be used to increase the EPR effect [43]. The infusion of Angiotensin II significantly elevates the mean arterial blood pressure by approximately 5.7 times. Interestingly, this increase does not correspond to the rise in blood flow to normal tissue [44]. Later, Li et al. confirmed that the EPR effect is amplified by hypertension generated by angiotensin II. Depending on the blood pressure reached, increasing the systolic blood pressure in tumor-bearing rats with angiotensin II infusion caused a selective increase in tumor blood flow volume by two to six times. The study's authors also noted a preferential buildup of medications with a molecular mass of less than 80 kDa inside the tumor tissue, in addition to the enhanced blood flow [45]. Taxanes stand out as one of the most effective pharmacological classes in the fight against cancer. The drug paclitaxel, for instance, has shown effectiveness against a wide range of malignancies. The most common cancers treated with taxanes include small cell and non-small cell lung cancer, ovarian cancer, and breast cancer. In 2005, the US FDA authorized a medication for the treatment of

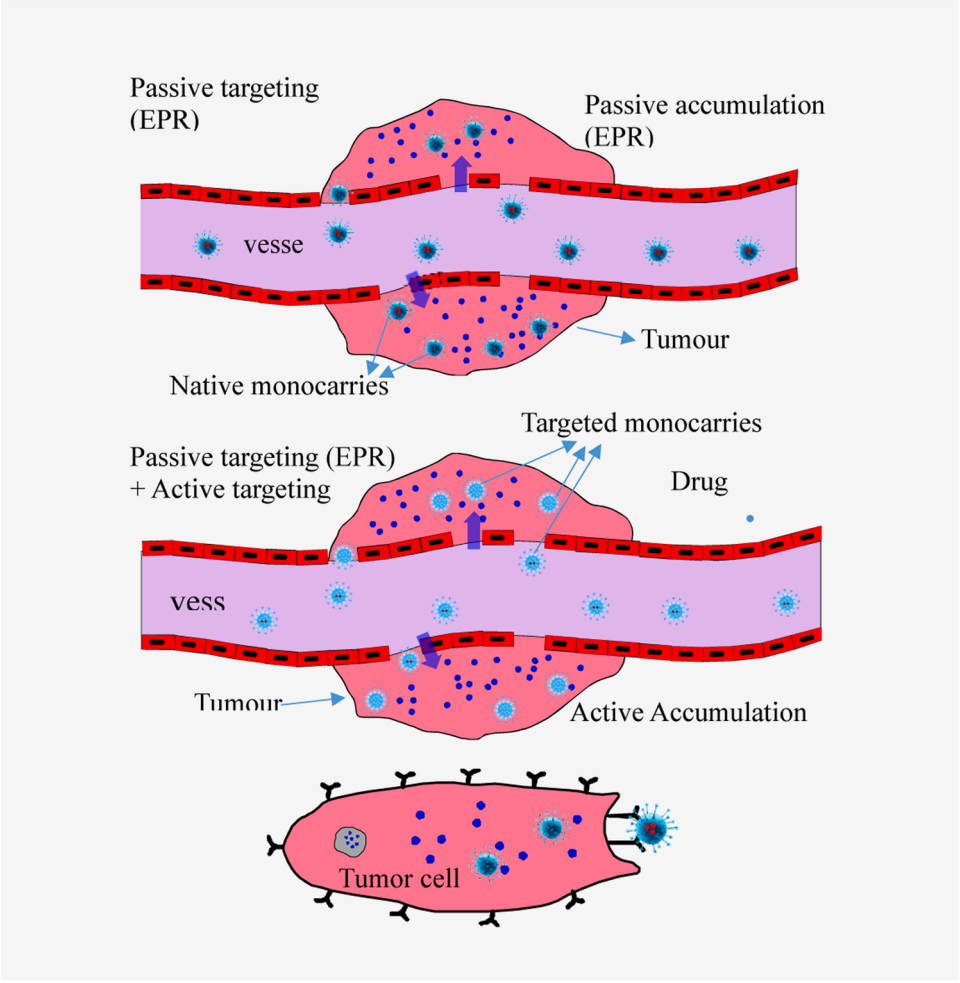

Fig. 1. Schematic representing active targeting (ICG) and passive targeting (EPR) of a tumor.

advanced or metastatic breast cancer (MBC) i.e. Abraxane® (albumin--bound paclitaxel, Abraxis Bio-Sciences). An anti-microtubule medication called Abraxane® works by stopping the depolymerization of microtubules and stabilizing them. It happens when a medication promotes tubulin dimer-based microtubule assembly. Microtubule rearrangement, which is essential for interphase and mitotic cellular processes, is hampered by this increased stability. The popular taxane paclitaxel causes aberrant microtubule arrangement and numerous asters during cell cycle and mitosis. In cases of pancreatic cancer, Abraxane® by itself or in combination with another cytotoxic drug like gemcitabine reduces the pancreatic stroma in Mice xenograft models [46].

2.2. Active targeting

NPs can only interact with their target cells when a ligand is attached to their surface [49]. Active targeting is vital in transporting genes, medications and theranostic agents to the target area while avoiding normal tissues, which increases therapeutic efficacy and lowers unwanted effects. Active targeting has the potential to significantly increase the quantity of medication given to the target cell when compared to free medicines or passively targeted Nano-systems [50]. When tumor site is accumulated, the active targeting enhances the treatment's efficacy. Ligands that are specifically bind to receptors that are overexpressed on tumor cells are coated on the Nano carriers' surfaces. Antibodies attached to the outside liposomes were the first to provide proof of this phenomenon in 1980 [51].

Active targeting in cancer therapy is not a one-size-fits-all approach. It offers a variety of strategies, each tailored to the unique features of the milieu surrounding the tumor microenvironment (TME). For example, the RGD peptide has been discovered for aVb3 integrin binding, a receptor overproduced in the TME vasculature and glioma cells. Similarly, the F3 peptide has been found to interact with the receptor of nucleolin on antigenic endothelial cells that are present in the TME. Even the tripeptide Asn-Gly-Arg peptide targets aminopeptidase N (CD13), a putative receptor in the TME. These strategies can directly target tumor cells, the moderately acidic TME, the vascularization of the TME, or the tumor nucleus. Folic acid (FA), a component of the TME, serves as a prototypical ligand due to its binding to the folate acid receptor (FAR).

Angiogenesis, developing new blood vessels, is a crucial process in cancer therapy. It is necessary for the growth of solid tumors., invasion, and metastasis. Without a sufficient blood supply, tumor growth is hindered, and the potential for spread is controlled. This is why anti-angiogenesis and blood supply blockage strategies are crucial in cancer therapy. Tumor cells express a range of pro-angiogenic chemicals, including transforming growth factor-α (TGF-α), platelet-derived growth factor, basic fibroblast growth factor, TGF-β, and vascular endothelial growth factor (VEGF), when angiogenesis is stimulated. Thus, one important area of focus for cancer therapy is targeted angiogenesis. Furthermore, the surface of tumor cells exhibits overexpression of a number of particular receptors linked to angiogenesis, such as matrix metalloproteinases, αvβ3 integrins, VEGFRs, and vascular cell adhesion molecule-1 [58,59]. A tyrosine kinase (TK) receptor belonging to the ErbB family, EGFR is overexpressed in a number of cancer forms, particularly those with squamous cell histology. The human SCC can be targeted by gold nanoparticles containing anti-EGFR-PEG-AuNPs and anti-IgG-PEG-AuNPs [60]. The therapeutic drug Herceptin® targets the overexpressed human EGF receptor-2 (HER2) on the surface of breast cancer cells. HER2-targeted PEGylated liposomal doxorubicin was developed in order to reduce cardiotoxicity, a known side effect of anthracyclines [61]. Additionally, a glycoprotein expressed on the surface of tumor endothelium that contributes to angiogenesis is called vascular cell adhesion molecule-1 (VCAM-1). In the model of breast cancer, NPs that target VCAM-1 have been identified in a study, suggesting a possible involvement for this protein [62]. Also, Vitamin B9, or folic acid, is essential for synthesizing nucleotides. The cells express the folate receptor responsible for internalizing folic acid. On the other hand, liquid cancer cells overexpress FR-β, On the other hand, tumor cells overexpress the alpha isoform of the folate receptor, or FR-α [63]. Moreover, the NPs have been used to target the folate receptors in specific cancer treatments [64].

2.3. Combination therapy

Resistance to cancer treatment is a continuous problem that necessitates the development of new combination medicines. Because of its ability to enhance the therapeutic efficacy, combination chemotherapy has been the standard of care for many types of cancer. It is widely accepted that synergistic actions, increased target selectivity and decreased cancer drug resistance can be achieved by strategically using pharmacological combinations [65]. The current cocktail dosing technique is a clinical norm, but it may be better. Combination chemotherapy has been considered the standard of care for several types of cancer. The use of NPs and chemotherapeutic medications at lower concentrations, eliminating undesirable cytotoxic effects, and greater efficacy are just some of the benefits of combination therapy, making it a potential cancer research method [66].

Camptothecin nanocrystals coated with hyaluronic acid were created using the antisolvent precipitation method. These nanocrystals enhanced the drug loading, stability, prolonged circulation, and water dispersion. The innovative potential of Nano-carriers cannot be overstated. Their ability to co-encapsulate various therapeutic drugs and coordinate their distribution to sick cells has garnered significant attention. Liposomes, polymeric micelles, polymeric NPs, and dendrimers are all examples of NPs systems. The response and survival rates achieved by combination chemotherapy are significantly higher than those achieved by single-agent chemotherapy. By combining numerous therapeutic agents with diverse physicochemical properties and pharmacological behavior, Nano formulations can overcome the challenges of multiple medicines with dissimilar pharmacokinetics and bio distribution due to differing metabolism rates. In this review study, we explore many NP technologies that have been used for the simultaneous encapsulation and administration of multiple drugs. This article aims to provide a comprehensive review of NP-based combination techniques for treating multidrug-resistant cancer [68–71].

One of the most promising strategies in cancer treatment is the delivery of two or more cytotoxic medications using nanoparticles. This approach has the potential to significantly increase the sensitivity of tumors to medicines [72]. Consequently, an additional anticancer strategy that has shown promise is the combination of cytotoxic medications with nucleic acids, which can lower dosage and reverse drug resistance [73]. Co-delivery of genes and gene agents, which results in the synergistic regulation of gene expression in tumor cells, is a recent trend in this field [74].

Second-generation drug carriers, such as nanostructured lipid carriers (NLC), represent a significant advancement in the field. Based on lipid nanoparticles, these carriers can precisely regulate drug release, thereby improving carrier stability [75]. Nanostructured lipid carriers' vast internal regulatory space enables them to administer hydrophobic medications [76,77]. Due to the distinct modes of action exhibited by Paclitaxel PTX and Doxorubicin DOX, the combination administration showed promising outcomes in treating solid tumors [78]. To investigate cytotoxicity in lung cancer cell lines that are not small cell, PTX and DOX nano lipid carriers using melt emulsification techniques were prepared. It was shown that the cytotoxic effects of PTX-DOX-NLC on lung cancer cells were three times more than those of NLC as a single drug and nine times better than those of the free drug formula, according to their viability data employing NCL-H460 cells. When PTX-DOX-NLC was compared to single-drug NLC, it demonstrated improved tumor targeting, more potent anti-tumor activity, decreased systemic toxicity, and increased effectiveness in preventing the growth of lung cancer. These findings point to an efficient approach for the targeted treatment

of lung cancer.

2.4. Liposomes

Liposomes are bilayer phospholipid vesicles that are typically round and amphiphilic. Liposomal formulations typically include phosphatidylcholine and phosphatidylethanolamine, whereas cholesterol is present to modify the membrane rigidity. Multi-lamellar vesicles (MLV) are often formed by rehydrating lipid sheets [79]. MLVs are then physically extruded into unilamellar vesicles. The ability of liposomes to encapsulate a wide range of pharmaceuticals, as well as their efficacy, biocompatibility, non-immunogenicity, and improved solubility of chemotherapeutic agents, make liposome-mediated drug administration an improvement [80]. Micelles and liposomes were the first to be used for drug delivery.

Lipoplatin, a liposomal version of cisplatin created by Regulon Inc., is being assessed for patients with non-small cell lung cancer in a phase III clinical trial. Furthermore, the incorporation of the drug into the polymer is represented by the exact core-shell nanostructures of cationic dendrimers, which have characteristics including chemical conjugation, surface adsorption, and interior encapsulation.

The pharmacokinetic and pharmacodynamics features of the therapeutic payload are improved by liposome-mediated drug delivery systems, promoting controlled and prolonged release of medications and decreasing systemic toxicity compared to free drugs. The therapeutic potential of liposomes as payload carriers and delivery vehicles is considerable [81]. A critical factor in this is the ability of nanoparticles to readily incorporate into liposomal membranes, thereby improving the stability, rigidity, delivery pharmacokinetics, and bioactivity of bioactive agents like drugs, proteins, and oligonucleotides. Phosphatidylethanolamine (PE), phosphatidylcholine, and cholesterol are liposome's most commonly used building blocks [82]. The versatility of liposomes is further demonstrated by their ability to encapsulate genes and medications in combination with lipids and other components, allowing them to carry nucleic acid agents and chemotherapeutic treatments [83]. Furthermore, the interaction between the loaded medicines and lipid carriers also impacts the tumors' co-delivery efficiency [84]. Generally, it forms complexes through the electrostatic contact between small interfering RNA and cationic liposomes. In addition, if the carrier is similarly charged, siRNA can be loaded into the liposome core [85,86].

To improve tumor penetration, Zhao et al. created a liposomal platform called (Deep learning model)D-L/si-DTX (docetaxel)that uses the pH-sensitive peptide DPRP(decidual prolactin-relaxed protein) to co-deliver DTX and Polo-like kinase (PLK-1-siRNA) for cancer therapy. The findings demonstrated that sufficient lysosome escape in the cytoplasm and cellular absorption was greatly enhanced by the liposome complex that is advanced and composed of DSPE-PEG2000-DPRP. Additionally, by improving penetration in tumor spheroids, D-L/si-DTX demonstrated tumor-selective administration and suppressed tumor growth. Compared to single-loaded liposomes, in vivo and in vitro studies showed that D-L/si-DTX could accurately deliver D-L/si-PLK-1 and stop tumor growth without causing adverse toxicity. This suggests that their suggested delivery platform could be a viable approach for combination therapy [87,88].

2.5. Polymeric micelles (PMs)

PMs are made up of graft copolymers or self-assembling amphiphilic blocks, and their average diameter ranges from 10 to 100 nm. Due to PMs' advantageous kinetic and thermodynamic properties, anticancer drug delivery has been targeted to tumors [89]. Amphiphilic polymers can reduce their free energy by assembling themselves into PMs in certain solvents. Micelles are beneficial because of their spherical shell-core shape, diminutive size, and ease with which they can be sterilized by filtration [90]. Due to the regulated release of PNP therapy, several chemotherapy medicines are amenable to PNP therapy. Regular micelles position themselves with an external hydrophilic portion and an interior hydrophobic core when they are in a polar solvent. The approach of targeted medication administration makes use of nanomicelles, which enhance the drugs' bioavailability and permit deeper tissue penetration [91]. Conversely, the reverse micelles are oriented in an opposite way in a non-polar solvent, with the hydrophobic portions facing the outside and the hydrophilic sections facing the inside. They are used for the delivery and encapsulation of hydrophilic medications, proteins such as lysozymes [92], and solutes such as fluorescein [93] and trypan blue [94]. The micelles' small size is a big advantage for drug targeting when compared to larger systems [95]. Amphiphilic molecule clusters have many advantages, such as enhanced solubility of scarce soluble chemicals, stability, and ease of sterilizing. Longer circulation times are made possible by the hydrophilic outer layer, which blocks steric hindrance and the construct from being identified and ensnared by the Reticular Endothelial System (RES) [96]. In order to facilitate active targeting, it also helps drive the conjugation with a ligand. The hydrophobic core of micelles created by van der Waals forces contains the lipophilic molecules grouped inside [97,98]. Polymeric micelles that self-assemble from amphiphilic block copolymers offer various physical and biological advantages over other nanocarriers, which have sparked significant interest in targeted cancer medication delivery. Their dimensions range from 20 to 100 nm, with a hydrophobic core facilitating effective drug loading for low-solubility medicines and a hydrophilic shell offering colloidal stability and the inherent sheath effect [99,100]. Polymeric micelles which are biodegradable are also perfect for hydrophobic anticancer medicines like doxorubicin (DOX) and paclitaxel (PTX) for targeted and regulated drug delivery [101,102]. These nanocarriers: (i) Increase the anticancer medications' water solubility. (ii) It can extend the duration of drug circulation. (iii)Tumor tissues can be passively targeted through the EPR effect. (iv) Increase bioavailability [103]. Possess outstanding biocompatibility and the ability to decompose in vivo into harmless substances that the body can absorb and eliminate. Because of their biodegradable nature, micellar solutions help regulate medication release and stop the long-term toxicity of drugs accumulating in human tissues [104].

2.6. Polymeric nanoparticles (PNPs)

Polymer NPs (PNPs) are the preferred platform for NP-based cancer drug delivery applications because of their versatility in modulating drug activity, delaying and controlling drug release, and increasing drug adhesion or duration in the skin [105,106]. Because of their solid, polymer-filled core, therapeutic payloads that are insoluble in water are more suited to polymeric NPs. Amphiphilic diblock copolymers are commonly used to self-assemble polymeric NPs. Natural polymers, including polysaccharides, polypeptides, and synthetic polymers like poly (lactic-co-glycolic acid) (PLGA), have been used to make polymeric NPs. PNPs, often having a diameter of less than 1 m, are categorized as either Nano spheres or Nanocapsules, depending on their chemical composition [107,108].

PNPs can be generated by one of two fundamental processes: the dispersion of premade polymers or the polymerization of monomers. PNPs are commonly utilized in targeted delivery systems for cancer therapy due to their fundamentally unique qualities, such as biodegradability, biocompatibility, nontoxicity, prolonged circulation, and a large payload spectrum of therapeutic medicines [28]. To improve compatibility with hydrophilic drugs [109–111], precisely control drug loading ratios, and precisely tune drug release sequence and kinetics, more advanced combinatorial drug encapsulation techniques have been developed through drug-polymer conjugations and particle functionalization. The cytotoxic medication DOX, the chemo sensitizer GG918, and the combination of DOX and GG918 were all delivered via novel polymer-lipid hybrid nanoparticle (PLN) formulations. A human MDR breast cancer cell line (MDA435/LCC6/MDR1) shows improved

encapsulation and therapeutic activity of DOX and GG918 when PLNs are present [112].

2.7. Dendrimers

Dendrimers are artificial macromolecules that share some characteristics with natural polymers, including a well-defined molecular structure, a mixture of functional groups, a nanoscale size, radial symmetry, and a structure that resembles the branches or limbs of a tree [113–115]. Dendrimers are hyper branched polymers that have a core surrounded by layers of repeating units and an outer layer of multivalent functional groups. The symmetrical, tree-like spherical shape has its origins in the center [116]. Dendritic polymers, which are similar to proteins, enzymes, and viruses, are easily functionalized and offer many benefits, such as increasing the stability of drugs that have been conjugated with dendrimers and reducing their immunogenicity and antigenicity. Because of their unusual combination of properties, dendrimers have attracted attention for use in a wide range of biomedical applications, such as drug administration, gene transfer, MRI contrast agents, and sensors [117–119].

Furthermore, the plan was to achieve MDR management using a PAMAM dendrimer. There are many descriptions available for DNA-assembled PAMAM dendrimers. The growth of epithelial cancer xenografts was greatly delayed by the produced dendrimers as compared to mice treated with single-agent chemotherapy [120].

2.8. Cancer imaging

According to the National Cancer Institute (NCI), nanotechnology has the potential to significantly improve cancer prevention, diagnosis, imaging, and treatment [121]. In clinical practice, various Nano-formulated drugs demonstrated highly targeted tumor delivery and were effective anti-cancer agent carriers [122]. Utilizing nanotechnology, it is possible to target tumors, detect pathophysiological abnormalities in tumors, deliver therapeutic medications, genes, or imaging agents, respond to external stimuli to release the agent, and track the therapeutic response. In addition, NPs have been used to identify imaging contrast agents, radioactive isotopes, chemical/-fluorescent dyes, and other imaging probes in cancer diagnostic imaging [123,124]. A significant advantage of using NP imaging agents as opposed to small molecules is the potential for preferential localization at the disease site due to increased permeability and retention. Therapeutic applications call for a biodegradable or rapidly excreted NP imaging probe with low toxicity and a strong imaging signal. Many NPs share a variety of obstacles that impede their therapeutic application development. NPs with prolonged blood circulation periods tend to congregate in the interstitial space of tumors after passing through leaking tumor blood capillaries. Tumor vasculature apertures are typically 400–600 nm, which is significantly larger than most normal tissues [125–127].

2.9. Therapeutic use of polymeric nanoparticles in cancer

Small-molecule drugs, peptides, proteins, and nucleic acids can all be put inside polymeric NPs and used as medicines. Liposomes, PNPs, and polymer micelles are all examples of PNPs. They can lengthen the time until a drug's effects wear off, making it more soluble and more selective for its intended targets [128,129]. Liposomes' limited ability to cure cancers resistant to many therapies stems from their poor ability to transport drug molecules into cells and control the timing of medication release [130].

Lipoplatin, a liposomal version of cisplatin created by Regulon Inc., is being assessed for patients with non-small cell lung cancer in a phase III clinical trial. Furthermore, the incorporation of the drug into the polymer is represented by the exact core-shell nanostructures of cationic dendrimers, which have characteristics including chemical conjugation, surface adsorption, and interior encapsulation.

3. Cancer imaging and treatment using multifunctional polymeric nanoparticles

Polymeric nanoparticles have been used as effective ways to deliver drugs to improve the effectiveness of therapy while reducing side effects. Photodynamic therapy (PDT) is a method of treating cancer that uses light and photosensitizers. Photosensitizers take in photons and send the energy to molecular oxygen, making singlet oxygen or other reactive oxygen species harmful to nearby tissues. Cons of PDT include phototoxicity to the skin and eyes and low tumor selectivity [131]. To kill tumor cells, scientists are now developing complex polymeric NP designs that can specifically target diseased tissues, pinpoint tumor locations, and release a variety of medications [132].

3.1. Nanoparticle quantum dots for cancer diagnosis and treatment

Semiconductor quantum dots (QDs) are being used increasingly as imaging and labeling probes. The natural fluorescence emission spectra of QDs span the 400–2000 nm [133]. For both diagnostic imaging and treatment, chemicals can be delivered in the form of QDs [134]. It has been reported that quantum dots (QDs) in photodynamic therapy (PDT) can work either as photosensitizers themselves or as energy donors that activate other photosensitizers [135,136]. QDs can generate singlet oxygen, but their quantum yield is much lower (5%) than that of a regular photosensitizer (40–60%) [137,138]. Because of their consistent composition, ease of manufacture, low cost, lack of toxicity when not exposed to light, and possible cytotoxicity when exposed to UV radiation, QDs make excellent photosensitizers. QDs can be engineered to emit in the near-infrared (NIR) spectrum, making them ideal for photodynamic therapy (PDT) of deep-seated cancers [139], in contrast to the vast majority of conventional photosensitizers, which emit in the visible spectrum.

4. In vitro studies

4.1. Cell viability and cytotoxicity assays

It is a common practice to evaluate the efficacy of the drugs before they become commercially available in the market. It has been observed that approximately a quarter of drugs fail to perform laboratory testing. Therefore, it is compulsory to evaluate the effectiveness of medicines for their effects in vitro and in-vivo experimental models [140]. Cell viability and cytotoxicity response of the NPs are majorly assessed on the cell cultures and by the following protocols. Many researchers have reported the LDH, MTT, MTS, Trypan blue, and Live and Dead assays as reliable methods for assessing the nanoparticle effects in cancer treatment [141]. As Song, Choi [142] has reported, the RH- (GFLG)3 with the formulated nanoparticles enhanced cellular uptake and negligible toxicity in Henrietta lacks (HeLa) cell lines using the MTT assay for cytotoxic effects. The MTT assay follows the calorimetric approach, and it is used to evaluate the cyto-viability at more sites. A previous study has assessed the silica NPs 15 nm in size in a dose-dependent manner for breast cancer where the 3-(4,5-dimethylthiazol-2-yl)− 2,5-diphenyltetrazolium bromide (MTT) used, and which turn into dark blue color Formazan indicated the reduced cell viability [143]. The MTT assay was also used to assess the mitochondrial activity and cell integrity for the efficacy of the drugs [144].

Another most widely reported approach in oncology is the Lactate dehydrogenase (LDH) assay, which analyzes the cell viability and cytotoxicity of the drugs in in-vitro studies, which is correlated with the high concentration of lactose dehydrogenase and the presence of the damaged cells in culture media [145]. Other assays, including the trypan blue and live and dead cells, are performed to determine the cytotoxic effects for both the tumor and normal healthy cells in the tumor

microenvironment. In the trypan blue assay, the trypan blue chemical penetrates the cells and stains the intracellular compartments. The results of this procedure indicate the presence of live cells in the experimental groups [146]. The live and dead assay is also used for cell viability analysis, in which the ethidium homodimer and calcein acetoxymethyl chemicals differentiate between the damaged and normal cells. The ethidium homodimer could only stain the cells whose cell membrane broke after toxicity [147]. Sayes and coworkers [148] have reported the gold nano-shell and fullerenes toxicity in human cell lines by using live and dead assays, where the ethidium only stains the damaged cells, which bind to the nucleus and colors the damaged organelles red. Using live/slow labeling on 4T1 tumor cells, the impact of p12 alteration on the cytotoxicity of liposomes containing doxorubicin and indocyanine green was assessed. As a result of improved cellular absorption, the results demonstrated that p12-modified liposomes significantly increased tumor cell death compared to non-modified liposomes. Moreover, the maximum level of cytotoxicity toward tumor cells was produced by the photothermal-induced structural breakdown of liposomes following near-infrared (NIR) laser irradiation. The viability of irradiated cells was assessed using the live/dead staining technique, and the proper and safe irradiation dosage was validated [149].

The bright-field microscopy method is used to visually observe the tumor cells' cell integrity and metabolic activity [150]. Most published data utilize These techniques to evaluate the effectiveness and side effects of the nanoparticles employed in cancer treatment. The apoptosis assay, ROS assays, oxidative stress enzyme tests, and NP evaluation are more approaches published for assessing cell survival.

4.2. Cellular uptake and localization studies

The internalization of nano-medicine in cancer and other tumor-related illnesses is significantly influenced by cellular uptake and its localization. The effectiveness of nano-drugs depends on the interaction with the extracellular environment and with intracellular components such as mitochondria and the nucleus. Many previous studies have mentioned that without the internalization of the anticancer drugs to infected tissues, these could not produce an immediate response against disease. NPs majorly worked in the targeted delivery of anti-cancerous medication at specific tumor sites [151]. Table 2 shows the types of NPs and their influence and cellular interactions depending on the type of NPs, such as organic (graphenes 6, carbon nano-tubs 8, carbon quantum dots ten and fullerene), inorganic (Metal oxide) [152,153] As many small size NPs show the higher cellular uptake than larger nanoparticles similarly the NPs with positive charge show the higher uptake by the tumorous cells. There are many factors, such as size, shape, charge density, hydrophobicity, and the presence of the functional group [154]. The weak interactions with the cell membrane result in collisions of nanoparticles with the cell membrane without facilitating the adhesion to the plasma membrane [155]. Many studies have reported the efficacy of the inorganic metal oxide NPs for their immunotherapeutic effects [156]. NPs migrate inside the cells through endocytosis, in which the clathrin-mediated endocytosis facilitates the movement of 100 to 350 nm NPs. However, the caveolin-1 protein-mediated target delivery is mainly responsible for the uptake of 20 to 100 nm NPs [157]. Phagocytosis and pinocytosis methods were also reported for the cellular uptake of nanomaterials [158].

Some NPs are investigated and reported for their beneficial utilization as anticancer drugs. For instance, cerium oxide is reported for its reactive oxygen species (ROS) scavenging abilities for normal bodily cells [159]. These NP therapies have revealed insights into cancer and normal cells for their cyto-viability and cytotoxicity [160]. Furthermore, the NPs could cross the blood-brain barrier, and this property allows many chemotherapies to reach the targeted organs [161]. However, these nanoparticles showed less migration for the highly packed cells akin to cancer cells. Therefore, further studies are needed for the investigation of NPs for the cellular uptake in tumorous tissues [162]. Also, these nanoparticles cause the production of ROS, which leads to cellular damage and induces apoptosis in normal cells.

Table 2
Presents the characteristic and mechanisms for organic and inorganic nanoparticles used in cancer treatment.

Nanoparticles	Characteristics	Mechanism	References
Inorganic Nanoparticles			
Zinc Oxide	Electrical sensitive semiconductor	ROS production and Cell wall internalization	[1]
Copper oxide	Antibacterial and catalytic properties	Enter the cell and detachment and membrane blebbing Cytotoxic	[2]
Graphene	Heat-sensitive, inexpensive, mechanical strength	Cause immunogenicity, Low retention	[3]
Quantum dots	Semiconductor, absorptive, photochemical stability	Invivo and invitro imaging, targeted gene delivery, tumor diagnosis	[4]
Titanium oxide	Bio-compatibility, retention effects, suitability	Partially enter the cell membrane, ROS production reduce proliferation, cell dyeing	[5]
Gold based NPs	Biocompatibility, surface plasmon resonance, easy synthesis	ROS concentration, cytokines release, apoptosis, use heat to destroy cancer cells	[6]
Silica based NPs	High surface area, adjustable pore diameter	Autophagy, ROS production, cell tracking	[7]
Nanoshells	Electrostatic stabilization	Kill the tumor cells and destroy the cancer cells, diagnosis of tumor	[8]
Organic Nanoparticles			
Polymeric NPs	Drug delivery, anti-inflammatory	Facilitate in Endocytosis, Ligand targeted delivery	[9]
Nanostructured lipid NPs	Increased solubility, low side effect	Active and passive delivery	[10]
Solid Lipid NPs	Assist in delivery of drugs	Reduce the development of cancer cell	[11]
Nanogels	Charge and softness, degradability, porosity	Ligand base delivery, enhance drug accumulation	[12]
Dendrimers	Branched, inner and outer shell, nano-sized and modifiable structures	Associated with the drugs and nucleic acid, conjugated mAbs	[13]
Chitosan NPs	Biodegradable and Nontoxic, biocompatible	Safe targeted delivery, safe unleash the huge amount of anticancer drugs, cellular immune response.	[14]
Liposomes	Biocompatible, Biodegradable	Increase the temperature of tumor cells, cause agglomeration, reduce toxic effects	[15]

4.3. Mechanistic studies

The NPs could move into the cells through passive and active migration. As in passive movement, the NPs move independently enhanced permeation and retention effects through the leaky channels [163,164]. In the NPs active targeting the nanoparticles conjugated with antibodies target specific receptors without the hindrance of vasculature and angiogenesis. In using these combined nanoparticles and chemotherapies, these particles work as the nano-carriers for anticancer drugs,

targeting the specific receptors, and also cause ROS production, leading the cancerous cells to cell arrest and to natural cell death. These conjugated molecules are designed according to the TME. Therefore, on the interaction with the specific receptors, these NPs unload the anticancer drugs into the TME. This nano-carrier is specifically designed as sensitive to the pH, temperature, hypoxic conditions, and interaction with specific enzymes for the tumor sites [165]. For instance, the amphiphilic polymer-based NPs release the drug upon encountering with highly acidic medium. Another study has reported that the copolymer polystyrene co-maleic anhydride conjugate with paclitaxel released the paclitaxel in an acidic environment where it exhibited tumor inhibition in Tumor-bearing BALB/ mice [166].

Similarly, Zhao and his colleagues [167] have reported acid sensitivity in PEGylated polyethyleneimine linked to Schiff base and conjugated with docetaxel, and indomethacin has shown the pH-based release under an acidic medium. Nanoparticles use another pathway where these tiny particles work against the vasculature in cancer. These NPs could target multiple tumors without hindering Enhanced Permeation and Retention (EPR) effects as they bound to specific antibodies for the particular overexpressed receptors in the cancerous tissues. Zhu and coworkers [168] have analyzed that the insoluble gel blocks the vessels, which causes the hypoxic condition. As a result, these hinder the migration of anticancer drugs to the target site; these NPs could pass these blocked vessels because of their tiny size and conjugated antibodies this NPs could pass this vasculature.

Some NPs target the alpha-v-beta-3 receptors, which are involved in cell-to-cell communication. It is reported in one research that the liposomes conjugated Doxorubicin (DOX) target alpha-v-beta-3 receptor showed increased therapeutic efficacy [169]. Gold NPs coated with chitosan with Sunitinib malate in the MCF-7 cell lines also showed higher cellular uptake and toxicity than free drugs [170]. Other NPs also target the different receptors involved in metastasis, such as CD105 endoglin glycoprotein, which is the growth factor targeted for cancer therapy using the nanoparticles [171].

Besides the role of NPs in the delivery of drugs the NPs also work as the therapeutic agent in leading the tumors to apoptosis without causing harm to normal cells. Some medications must be delivered to organelles where these NPs also enhance the oxidative stress and inhibit topoisomerase II, leading to apoptosis at the cancer site with minimized side effects [172]. The preclinical studies for micelles loaded with docetaxel were used to target prostate cancer, which shows increased circulation time and low accumulation in the liver of patients [173].

Overall, the anticancer medications' toxicity towards healthy organs is reduced by the NPs, which are mostly utilized for targeted distribution as conjugated antibodies. Yet, certain NPs disrupt the cell cycle, induce oxidative damage, and increase the effectiveness of using NPs in combination with anticancer medications. Overall, the results of mechanistic investigations suggest that NPs as a promising therapy approach for cancer because of their capacity to target and transport drugs only to cancer cells while posing the least amount of harm to healthy cells. Overall, Fig. 2 Illustrates the traditional use of the NPs in cancer therapeutics, as it has been used to detect biomarkers, locate cancer cells, and reduce the toxicities of chemotherapies by active and passive drug delivery of anticancer medicines. Furthermore, polyoxyl 15 hydroxy stearate micelle has the potential to dramatically increase myricetin's antioxidant activity in vitro and speed up membrane permeability for myricetin's optical transport [174]..

4.4. In-vitro applications of protein nanoparticles

Protein-based nanoparticles have several advantages, including easy manufacturing, high medicine binding capacity, lack of toxicity, lack of immunogenicity, biocompatibility, biodegradability, and plasma half-life [175–177]. Targeted ligand binding and other surface modifications are made more accessible by the functional groups on the surfaces of protein nanoparticles, which act as intelligent nanoparticles [178,

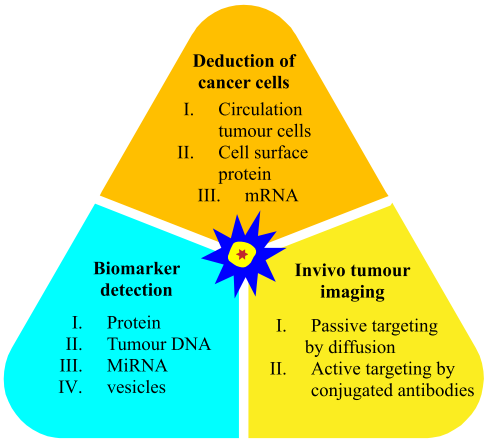

Fig. 2. shows the approaches for Nanoparticles in cancer therapeutics.

179]. One of the most important proteins in plasma, albumin, has been used in a number of medical applications within the last few decades. When administered to neuroblastoma cell lines, Dox-loaded human serum albumin nanoparticles were found to have superior in vitro anticancer activity compared to the pure drug [180]. Bovine serum albumin nanoparticles loaded with PTX are created by dissolving and coating folic acid., have been recognized to target human prostate cancer cell lines [181] effectively. Protein nanoparticles function as an efficient, noncovalent, reversible carrier of hydrophobic substances, enabling their passage through physiological fluids and discharge at the surface of the cell. Furthermore, Glycoprotein receptor interactions with protein can facilitate the transcytosis of molecules associated with albumin [182]. Abraxane, a medication with a diameter of roughly 130 nm, is the first pharmaceutical product authorized by the FDA for commercial use that has demonstrated notable efficacy in treating metastatic breast cancer [183].

4.5. A54 peptide

In a phage display random peptide library, the hepatic carcinoma can be bound by the A54 peptide. For the BEL-7402 human hepatoma cancer cell line, it is the most effective peptide. As a result, a target ligand for liver cancer is the A54 peptide. Polyethylene glycol 1000 vitamin E succinate, or A54-TPGS, was esterified by Zhang et al. and mixed with calcium phosphate nanoparticles to create a multifunctional drug-carrying system with enhanced tumor tissue homing characteristics and an extended tumor tissue residency duration [184]. Du et al. synthesized the PEGylated stearic acid grafted chitosan micelle (PEG-CS-SA), which was functionalized with the A54 peptide acting as a targeted ligand. In vitro, it demonstrates a unique ability to internalize liver cancer cells, and in vivo, it has a wide spread capacity in the liver and liver cancer tissues. It can lessen toxicity and suppress tumor growth more successfully [185]. According to research, artesunate (AS) has a potent cytotoxic effect on tumor cells both in vivo and in vitro. It is activated by iron within cells. As a result, Hou et al. used thin films as an anchor on the surface of artesunate-loaded copper sulfide nanoparticles as a targeting molecule. Through tf-mediated endocytosis, the system can preferentially target tumor cells and allow breast cancer cells to absorb them. As it delivers iron ions and As to the tumor, it enhances antitumor activity [186].

5. In vivo studies

5.1. Efficacy studies in animal models

Because of their unique characteristics, such as their small size and large surface area, which allow for effective drug delivery to cancer

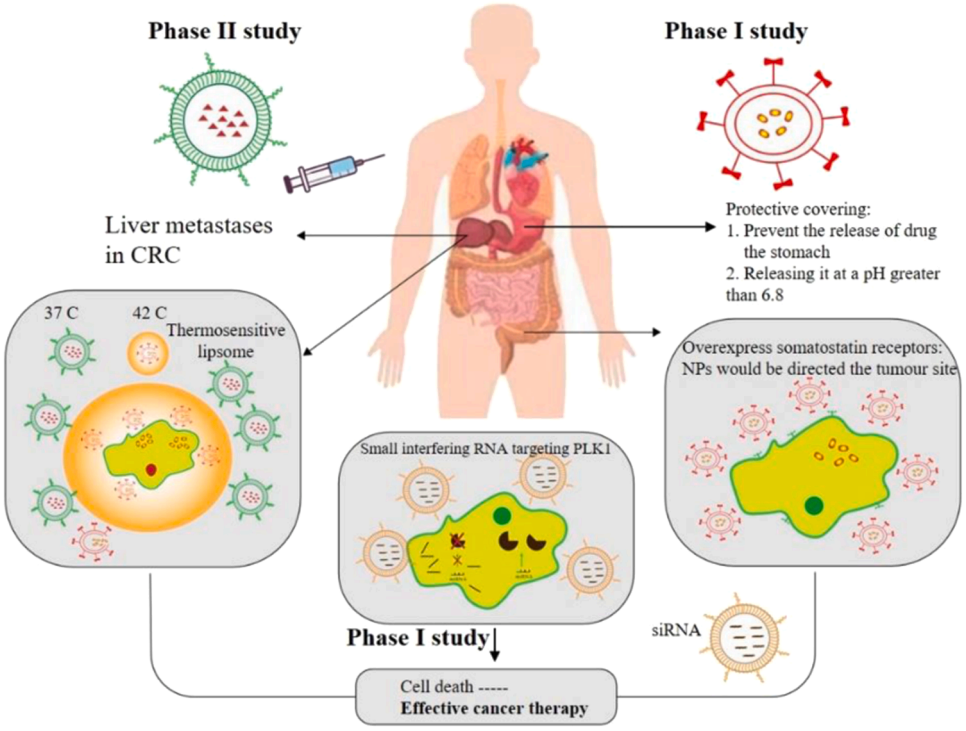

Fig. 3. Representative Image shows a clinical trial that used nanoparticles to treat pancreatic cancer that had become resistant to other treatments. (a) Thermodox shows the smooth-thermosensitive liposomal NPs carrying intravenous doxorubicin-one in the open phase II study NCT02181075. (b) Cetuximab loaded in polymeric NPs coated with somatostatin is administered orally in an open phase I study NCT03774680. (c) The LNP with siRNA TKM-080301 targets the PLK1 protein.

cells, NPs have become an attractive therapeutic approach for cancer treatment. Several factors influence the efficacy of NPs in cancer therapy, including their physicochemical characteristics, tumor-targeting strategies, and their therapeutic effects [187]. The EPR effect, which allows for the passive deposition of NPs in tumor tissue via leaky blood vessels, is an essential factor influencing NP efficacy [188]. Furthermore, NPs can be designed and synthesized with targeting ligands like antibodies or peptides that can vigorously attach to particular receptors on cancer cells, allowing for the selective delivery of therapeutic agents to tumor tissue [189]. Furthermore, NPs can overcome multidrug resistance (MDR) in cancer cells by simultaneously delivering multiple drugs or by inhibiting efflux pumps that cause drug resistance [190]. Pharmacological treatments with nanoparticles have additionally been demonstrated to have synergistic activity, resulting in improved cancer therapeutic response [191]. NPs, for example, can be used to deliver chemotherapeutic drugs in combination with immuno-stimulatory agents or gene therapy vectors, enhancing the immunologic reaction against cancer cells and improving overall clinical outcomes [192]. NP efficacy in cancer treatment has been demonstrated in preclinical and clinical studies. Mao and his co-workers studied the acute toxicity of submicron mesoporous bioactive glass microspheres (SMBGs) in Institute of Cancer Research (ICR) mice following intravenous injection of SMBGs 20, 100, and 180 mg/kg over 14 days, and they found that the LD50 of SMBGs was more significant than 250 mg/kg. They also found that no death or aberrant behavior was noticed in any of the experimental animals, indicating that the in vivo toxicity of SMBGs is low in groups [193].

Similarly, liposomal doxorubicin and paclitaxel, for example, have been granted clinical use in breast and ovarian cancer [194], respectively. Additionally, the carbon nanotube (CNT)-ABT737 nano drug-coated in polyethylene glycol targets explicitly the mitochondria of lung cancer cells; the researchers created a lung cancer cells experienced apoptosis as a consequence of the nano drug's delivery into early endosomes and delivery into the mitochondria [195]. According to the study's findings, using this nano-drug to better target the mitochondria of anticancer Nano drugs for the fight against lung cancer may be a successful technique.

However, there are several limitations and challenges associated with NP-based cancer therapy, such as concerns about toxicity and biocompatibility, low capacity for loading drugs, and a lack of standardized procedures for NP production and characterization. Many studies reported their side effects in in-vivo studies. For instance, Sybille and his colleagues analyzed the pulmonary toxicity and respiratory persistence of Ge-imogolite nanomaterials in rats. Ge-imogolite from SW and DW was shown to cause a more severe inflammatory and fibrotic response than crocidolite after exposure for 60 days [196]. In another study, the in vivo experiment used zebrafish embryos to test the viability of using Au NPs as probes for embryonic imaging. The study has shown that Au NPs affected zebrafish embryos in real-time and discovered that the random distribution of Au NPs throughout the source led to harmful effects that were mostly stochastic. This implies that there may be restrictions on the use of Au NPs for imaging the developing fetus due to the possibility of unforeseen harmful consequences. The viability and safety of utilizing Au NPs as probes for embryonic imaging require more investigation [197]. This emphasizes the significance of carrying out lengthy toxicology studies to comprehend any dangers related to the usage of NPs.

Several clinical research trials with an emphasis on combination therapy were made possible by the advantages of functionalized nanocarriers, including their enhanced drug loading for targeted modification, passive targeting ability, enhanced permeation and retention, and a high surface-to-volume ratio [198]. For example, phase 1 clinical studies have only produced modest results from the safe and effective nanosized formulation demonstrated by Katragadda et al. for the delivery of paclitaxel and 17-AAG combination therapy [199].

Liu et al.'s novel nanoparticles for pulmonary transport were developed utilizing two anticancer medications encapsulated into polymeric microspheres drugs. Research conducted on the in vivo pharmacokinetics and biodistribution of the microspheres demonstrated their extended half-life and potential for lung development [200]. Also,

the Tyrosine kinase inhibitors are utilized in clinical practice to treat solid tumors, as reported by Araujo et al. [201]. Moreover, tyrosine kinase SRC (proto-oncogene tyrosine-protein kinase) is a promising therapeutic agent for treating solid tumors since it is essential to both the oncogenic and bone-metastatic processes. Determining whether targeting SRC is an effective therapeutic method is made more accessible by the current discoveries and one of the SRC inhibitors that are currently being developed. Both in vitro and in vivo experiments showed that the NPs had a better antitumor impact and were less harmful [202,203].

5.2. Cell membrane coated nanoparticles

Using a biomimetic approach, therapeutic devices with a nanoparticle core coated in a membrane derived from different cell sources—such as cancer cells, stem cells, platelets, or white blood cells—are made using cell membrane-coated nanoparticles [204,205]. The standard procedure for creating CMCNPs involves isolating plasma membranes from different cell sources and incorporating core nanoparticles into membrane vesicles. Recently, there has been a lot of interest in these biomimetic CMCNPs because of their tailored nanomaterials and advanced smart nanoparticles for cancer therapy [206]. For instance, it is possible to generate platelet membrane-coated nanoparticles with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) placed onto the outside membrane and Dox loaded into the inner nanoparticles. Platelet membrane-coated nanoparticles demonstrated the highest level of anticancer efficacy in an animal model with a subcutaneous tumor and a metastatic location [207].

5.3. Gold nanoparticles

Doctors can easily distinguish between tumors and healthy cells thanks to the way that gold nanoparticles reflect light after being injected and adhere only to malignant cells [208]. Photothermal therapy (PTT) has gained more attention lately due to the near-infrared absorption of gold nanoparticles [209]. A multifunctional nanoplatform based on Ti3C2-MXene Au nanocomposite was proposed by Chang et al. in addition to photoacoustic (PA) and thermal dual-mode imaging in vivo. This enabled the triune of PTT/enzyme kinetics treatment/antitumor immune therapy [210].

5.4. Prostate-specific membrane antigen

Prostate cancer cells overexpress PSMA, a transmembrane glycoprotein known to be a biomarker for the disease. Cho et al. developed a multifunctional nanosystem to inject anti-prostate-specific membrane antigen (anti-PSMA) into the paclitaxel-loaded composite nanocarrier. The hybrid nanoparticles were effectively guided into the tumor area and LNCaP cells both in vivo and in vitro through the targeted receptor PSMA [211].

5.5. C16Y peptide

The αvβ3 integrin also targets the C16Y peptide. Negishi et al. examined the targeting capability of C16Y-L liposomes, which they modified using the C16Y peptide, both in vitro and in vivo. It can preferentially adhere to tumor slices and has better cellular absorption in colon 26 cells than liposomes. According to in vivo research, C16Y-L builds up in tumor blood vessels and tissues. This demonstrates the precise tumor targeting of the C16Y peptide.

5.6. Pharmacokinetics and bio-distribution studies

NP distribution and clearance in vivo are critical experiments for understanding their behavior within the body. Researchers can gain valuable insights into how NPs are digested and eliminated by the body by monitoring their localization in different tissues and organs over time and analyzing their metabolism and excretion. This data is critical for optimizing NP-based treatments and diagnostics and identifying potential cytotoxic effects or other challenges. Finally, in vivo, nanoparticle distribution and clearance enable the development of safe and effective nanoparticle-based technologies for various biomedical uses. There are numerous methods for studying in vivo distribution. NPs containing definite functional groups, for example, can be identified using atomic absorption spectrometry (AAS), inductively coupled emission spectrometry (ICP-AES), ICP-MS, and other techniques [212]. The study's findings revealed that AS1411-CS/rGO/Ag+ -DNA initially accumulated in the liver and lung after entering the body and then transferred to the tumor site. Huang, Zhong, Li, Wu, He, Tang, Tang, Su, Feng, and Wang [213] used ICP-MS to detect AS1411-CS/rGO/Ag+ -DNA in various organs (heart, liver, spleen, lung, and kidney) and tumor tissues after 0 h, 12 h, 72 h, 216 h, 288 h. The integration of fluorescent substances into nanoparticles enables tracking there in vivo distribution and localization. CaO2 @CuS-MnO2 @HA (CCMH) nanocomposites in 4T1 tumor-bearing mice were observed by Huang, Lin, Chen, Wang, Lin, Liu, Ren, Tao, Zhao, Xu [214] using the small animal in vivo fluorescence imaging at various time points. After 6 h, the results showed that CCMH accumulated most significantly at the tumor site.

Different nanoparticles used for cancer or tumor treatment showed different pharmacokinetics and efficacy rates in different animal models. The effectiveness of NP formulations containing docetaxel (DXL) in Wistar rats was investigated in this study. The results showed that these NPS formulations had approximately three times the relative bioavailability of the DXL control. Compared to DXL, the pharmacokinetic profile of DXL-CS-F-Ctmab-NP showed an increased half-life and mean residence time [215]. Similarly, another study has reported that ultra-small porous silica NPs (USPN) conjugated with the isotopic pair 90/86Y could be used for cancer imaging and therapy. The USPN demonstrated excellent pharmacokinetics, with lengthy blood circulation and elevated tumor-to-muscle and tumor-to-liver uptake values. The USPN was found to accumulate significantly in the tumor (12% ID/g) while trying to evade the reticuloendothelial system (RES) organs using in vivo PET imaging [216].

In another study, the two NPs showed a different bio-distribution rate where the passive tumor targeting ability of TiN and TiN-PEG NPs was tested in a murine model using EMT6/P mammary carcinoma cells. NPs were injected when the tumor size was 300 100 mm3, and their pharmacokinetics and bio-distribution were studied using ICP-MS. TiN NPs with a short half-life in the bloodstream were detected in the bloodstream. TiN-PEG NPs, on the other hand, had increased circulation time and were detected in the bloodstream 1 h after administration, indicating that PEGylation improved the colloidal stability of the NPs under physiological conditions [217]. Although nanoparticles offer considerable potential for targeted medication administration and increased therapeutic efficacy, their pharmacokinetic characteristics must be thoroughly evaluated and tuned to guarantee safe and successful usage. Size, shape, surface chemistry, and bio-distribution are only a few elements that affect how pharmacologically active NPs are in living organisms. The reported knowledge of the pharmacokinetics of NPs and their potential application in the treatment of cancer is expected to continue to grow as a result of ongoing research in this field.

5.7. Clinical trials

On a worldwide basis, researchers are still looking for an alternative to chemotherapy and other ineffective cancer treatments. NPs are already widely used in the medical industry, even if efforts to use nanotechnology to cure cancer and boost the potency of medicines are still in the development stages. NPs have a relatively high surface area because they are so small and have unique properties. Because of this, they can work well with a wide range of ligands, such as DNA, peptides, RNA, aptamers, and antibodies [196]. So, the changed NPs are more likely to reach where they need to go (in vivo). NPs can be used with a

broader range of theranostic elements to improve their pharmacokinetic properties and, as a result, their effectiveness in treating cancer [218]. Researchers are also looking into how NPs can be used as immunogenic cargo in traditional radio- and chemotherapies and cutting-edge adjuvant therapies. Nano-artificial antigen-presenting cells (Nano-aAPCs) have the potential to be among the most sophisticated cancer nanomedicines [219 because, like aAPCs used in cancer immunotherapy [220], they mimic the antigen-presenting cell by stimulating essential signal proteins that fight carcinoma. By modifying the expression of genes involved in a broad range of biological processes in tumor cells, NPs have the potential to be used to treat cancer. Many genes are controlled in (human lung cancer cells) A549 cell lines to have an anticancer impact, including PCBP2, HNRNPL, ATF3, RAB5C, NFKB2, EIF3I, NKIRAS2, PIAS4, RRAS, STAT3, AKT1, SRC, EIF2C2, HRAS, CDC34, and EIF5A [221]. Some of these genes have been appropriately identified as molecular markers due to their overexpression in cancer cells. Due to the possible anticancer effects of Fe3O4 nanoparticles on cancer-specific molecular markers, gene therapy may have broader applications and implications.

Even though Nano formulations are routinely used in medicine, there aren't many clinical types of research examining how effective they are for colorectal rectal cancer (CRC). TKM-080301 is made up of tiny liposomal NPs that contain small interfering RNA directed against the protein PLK1. PLK1 is a protein that helps control the different stages of mitosis and is found in high amounts in some tumor cells [222]. Rectal cancer (NCT02010567) treatment possibilities for CRLX101, a nanoparticle made of camptothecin attached to a biocompatible copolymer of cyclodextrin and polyethylene glycol (PEG), have been investigated. Compared to free camptothecin, CRLX101 significantly increased therapeutic efficacy and lowered gastrointestinal toxicity when coupled with standard chemotherapy. Hence, CRLX101 may provide a new alternative for treating rectal cancer by improving the efficiency of neoadjuvant chemotherapy [223].

Around this time, clinical research (NCT01375816) evaluated the effectiveness of 5-fluorouracil leucovorin irinotecan (FOLFIRI) and PEP02 (FUPEP) in patients with spreading CRC who had previously had oxaliplatin (OXA) treatment. PEP02, a liposomal nanoformulation of irinotecan (IRI) hydrochloride, is used. Bevacizumab was approved for usage by both groups. In the study population (n = 55), the 2-month response rates for FOLFIRI and FUPEP were 7.4% and 10.2%, respectively. The most frequent side effects at higher severity levels were diarrhea, mucositis, neutropenia, and grade 2 baldness (similar for both arms). Silica NPs are being studied in an open phase I study (NCT02106598) to more accurately map nodal metastases, which might result in more effective metastasis removal. These fluorescent cRGDY-PEG-Cy5.5-C dots (A fluorescent imaging agent made of silica nanoparticles surrounded by polyethylene glycol (PEG) chains connected to cyclo-[Arg-Gly-Asp-Tyr] (cRGDY) peptides and tagged with the near-infrared fluorophore cyanine 5.5) on the silica NPs allow for the detection of tumor cells in nodules before surgery [224].

Thermodox is a lipid-encapsulated doxorubicin (DOX) that is both stable at high temperatures and sensitive to heat, making it ideal for thermal ablation. A randomized, controlled phase II open research study assessed the effectiveness, safety, and practicability of employing Thermodox in conjunction with temperature ablation to cure liver metastases in colorectal cancer (NCT02181075). The primary goal of temperature ablation is to eradicate the tumor's core, whereas DOX improves the treatment outcome by focusing on the tumor's periphery [225]. A disadvantage of mitomycin C, a very effective chemotherapy drug with minimal resistance rates, is its toxicity. As part of phase I clinical investigation (NCT01705002), the safety profile of a mitomycin C nanoformulation PEGylated Liposome (PROMITIL) given intravenously to patients with solid malignancies, such as metastatic CRC, was assessed. The well-tolerated dosing range of PROMITIL was much more comprehensive than that of free mitomycin C [226]. Also, in patients with advanced CRC with the KRAS (gene) mutation, phase II clinical research (NCT00931840) assessed the effectiveness, safety, and tolerability of a water-soluble PEGylated SN-38 molecule, a topoisomerase inhibitor [227], in combination or not with cetuximab.

Compared to IRI plus cetuximab, the combination of EZN-2208 and cetuximab was well tolerated but did not significantly increase overall survival or progression-free survival. In a different open-label phase I trial (NCT03774680), polymeric NPs loaded with cetuximab and a somatostatin analog are being assessed. Targeting cancer cells using somatostatin-coated NPs may be successful [228]. These NPs were given orally to CRC patients, shielding the medication from the stomach's acidic pH and releasing it at a pH of around 6.8. Because of the exceptionally high density of somatostatin receptors on CRC cancer cells, the NPs would be directed there. The amino acid arginine, which is necessary for the survival of cancer cells, is swiftly degraded by the anticancer drug arginine deiminase (AD). Free AD is highly immunogenic because of its *Mycoplasma* origin, which means certain persons may have allergic responses [229]. AD is thus not broadly applicable; however, it may be less immunogenic if it were encapsulated. In the phase I/II clinical study, AD-PEG20, a Nano formulation of AD with PEG, was investigated with Folfox for patients with advanced gastrointestinal cancers (NCT02102022). Nano-encapsulated immunotherapy clinical studies have not been conducted on CRC patients. Yet, clinical research will soon begin examining this approach with advanced solid tumors. Patients with advanced CRC are a good fit. In phase I clinical studies (NCT03781362), the Food and Drug Administration (FDA) approved using CPI-100 in patients with metastatic solid tumors in 2018. The immunostimulatory and anticancer medicines are included in the NPs CPI-100 based on the preparation of coordination polymers are going to be used.

The selectivity of chemotherapy treatments or conventional or herbal medicines has improved by conjugating different proteins or short peptides to the surface of NPs. The serum glycoprotein transferrin was the most often used ligand. Enhances iron transport from the blood into cells by binding to the transferrin receptor on the cell surface. Higher transferrin receptor levels have been linked to cancer cells' ability to spread and resist treatment [230]. Conjugated transferrin NPs for chemotherapy have been proven to improve the cytotoxicity of the drugs and their uptake by cancer cells in vitro and in vivo. Delivery of hydroxyl camptothecin via a transferrin-conjugated polyethylene glycol (PEG) NPs resulted in increased in vivo growth inhibitory activity against the S180 tumor, enhanced drug accumulation in cancer cells, and an extended half-life in circulation compared to non-targeted NPs.

Research using transferrin-conjugated chitosan-PEG nanoparticles carrying paclitaxel showed an enhanced cytotoxic impact against transferrin-overexpressing human non-small cell lung cancer cells [231]. The arginine-glycine-aspartic acid peptide has been added to the surface of NPs in addition to transferrin to target the integrin V3 receptor specifically. This receptor plays a crucial role in promoting tumor development, metastasis, and angiogenesis and is found on the surface of tumor vessels and several cancer cell types [232]. Several RGD-conjugated NPs have been developed and demonstrated to facilitate the delivery of conventional or herbal remedies or chemotherapeutic drugs to cancer cells. While testing the cytotoxic effect of paclitaxel against integrin V3-overexpressing human glioblastoma cells, a cyclic arginine-glycine-aspartic acid-tyrosine-lysine (RGDyK)-conjugated poly (trimethylene carbonate)-PEG micellar NP was shown to be superior to non-targeted NPs (U87MG). Inhibition of cell death by targeted NPs was more significant than that seen with non-specific ones (11.23% vs. 8.31% and 8.03% vs. 5.38%, respectively). As a percentage of the total medicine supply, 6.67% and 4.32% (mean values) were given out free of charge. Medication absorption was also shown to be enhanced in U87MG cells.

In addition, doxorubicin-delivering RGD-conjugated magnetic iron oxide nanoparticles (MIONPs)-PEG displayed improved cellular absorption and cytotoxic activity against integrin V3-overexpressing human cervical cancer cells compared to free drug and non-targeted

MIONPs (HeLa). Further studies have shown that cRGDyK-conjugated poly(2-ethyl-2-oxazoline)-poly(D, L-lactide) NPs used for paclitaxel administration were more toxic to cells compared to non-targeted NPs and free drug (mean IC50: 51.16 ng/mL, 64.53 ng/mL, and 62.95 ng/mL, respectively). Increased activity was achieved by enhanced cellular absorption and specific targeting of prostate cancer cells (PC-3) that overexpress integrin V3. In mice bearing the PC-3 tumor, the targeted NP was also found to hasten the suppression of tumor formation in vivo [233].

To increase the selectivity of chemotherapeutic drugs for cancer cells, peptides have been connected to the surface of NPs. Two examples are bombesin peptide-conjugated poly (lactic-co-glycolic acid) (PLGA) and NR-7 peptide-conjugated PLGA-PEG NPs. The use of these NPs has enhanced the selection of chemotherapeutic drugs for cancer cells. Prostate, breast, ovary, pancreatic, and colorectal cancers, all of which overexpress gastrin-releasing peptide receptors, are primary targets for bombesin-conjugated NPs carrying docetaxel [234,235]. Human breast cancer cells (MDA-MB-231) that overexpress the gastrin-releasing

Table 3
The below table shows the summary of studies that looked at how active targeting nanoparticles (NPs) could be used to deliver chemotherapeutic drugs to treat cancer.

Name	Drug-NP platform	Types of study	References
H2009.1 peptide	Doxorubicin-liposome	In vivo: human non-small cell lung cancer cell lines (H2009) xenograft	[44]
AP-1 peptide	Paclitaxel-cyclodextrin	In vivo: human breast adenocarcinoma cell lines MDA-MB-231 xenograft	[45]
Peptide CVKTPAQSC	Docetaxel-PLA	In vitro: human lung cancer cell lines (A549) In vivo: cell lines A549 xenograft	[46]
Transferrin	Hydroxycamptothecin-PEG	In vivo: murine sarcoma cell lines (S180) xenograft	[47]
Transferrin	Paclitaxel-PEG-chitosan	In vitro: non-small cell lung cancer cell lines (HOP-62)	[48]
RGDS	Doxorubicin-PEG-MIONP	In vitro: human cervical carcinoma cell lines (HeLa)	[49]
cRGDyK	Paclitaxel-micelle	In vitro: human prostate cancer cell lines (PC-3) In vivo: cell lines PC-3 xenograft	[50]
RGD	Doxorubicin-dendritic poly-L-lysine-gelatin	In vitro: mouse mammary breast tumor cell lines (4T1) In vivo: cell lines 4T1 xenograft	[51]
Bombesin peptide	Docetaxel-PLGA	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	[52]
NR7 peptide	Doxorubicin-PLGA-PEG	In vitro: human ovarian carcinoma cell lines (SKOV3) In vivo: cell lines SKOV3 xenograft	[53]
LHRH peptide	Methotrexate-HSA	In vitro: human breast carcinoma cell lines (T47D)	[54]
Angiopep-2	Doxorubicin-dendritic poly-L-lysine-gelatin NP	In vitro: mouse mammary breast tumor cell lines (4T1) In vivo: cell lines 4T1 xenograft	[55]
Hyaluronic acid	Doxorubicin hydroxylapatite	In vitro: human hepatocellular carcinoma cell lines (HepG2) In vivo: cell lines HepG2 xenograft	[56]
Hyaluronic acid	Doxorubicin-HACE-PEG	In vitro: murine squamous cell carcinoma cell lines (SCC7) and mouse embryo fibroblast cell lines (NIH3T3) In vivo: cell lines SCC7 xenograft	[57]
Hyaluronic acid	Doxorubicin hyaluronic acid-Lys-LA10	In vitro: doxorubicin-resistant human breast adenocarcinoma cell lines (MCF-7/ADR) In vivo: cell lines MCF-7/ADR xenograft	[58]
Hyaluronic acid	Doxorubicin-PBLG-LA	In vitro: human breast adenocarcinoma cell lines (MCF-7) In vivo: cell lines MCF-7 xenograft	[59]
Folic acid	Docetaxel-PEG-PLGA	In vitro: human cervical carcinoma cell lines (HeLa) In vivo: cell lines HeLaxenograft	[60]
Folic acid	Doxorubicin-dendrimer	In vitro: human epidermal carcinoma cell lines (KB)	[61]
Folic acid	Gemcitabine-BSA	In vitro: human ovarian cancer cell lines (Ovcar-5) and human breast adenocarcinoma cell lines (MCF-7) In vivo: Ehrlich ascites carcinoma tumor cell-bearing mice	[62]
Folic acid	Carboplatin-PLGA-chitosan	In vitro: human cervical carcinoma cell lines (HeLa)	[63]
Folic acid	Doxorubicin-PEG	In vitro: human epidermal carcinoma cell lines (KB), human lung cancer cell lines (A549) and human hepatocellular carcinoma cell lines (HepG2) In vivo: cell lines KB xenograft	[64]
Folic acid	Cisplatin-PEG-MSN	In vitro: human cervical carcinoma cell lines (HeLa)	[65]
Folic acid	Doxorubicin-β-cyclodextrin	In vitro: human placenta choriocarcinoma cell lines (JAR), human colon adenocarcinoma cell lines (HT-29), human breast adenocarcinoma cell lines (MCF-7), and mouse fibroblast cell lines (3T3)	[66]
Folic acid	Paclitaxel-PEG-PLGA	In vitro: human endometrial carcinoma cell lines (HEC-1A) In vivo: cell lines HEC-1A xenograft	[67]
Anti-Fas mAb	Camptothecin-PLGA	In vitro: human colorectal cancer cell lines (HCT116)	[68]
Anti-CD20 mAb	Doxorubicin-DSPE-PEG2000	In vitro: human Burkitt's lymphoma cell lines (Raji)	[69]
Anti-CD47 mAb	Gemcitabine-MIONP	In vitro: human pancreatic ductal adenocarcinoma primary cells (Panc215 and Panc354)	[70]
EGFR antibody	Rapamycin-PLGA	In vitro: human breast adenocarcinoma cell lines (MCF-7)	[71]
PR81 mAb fluorouracil	5- -BSA	In vitro: human breast adenocarcinoma cell lines (MCF-7)	[72]
Aptamer AS1411	Doxorubicin-HPAEG	In vitro: human breast adenocarcinoma cell lines (MCF-7)	[73]
Aptamer AS1411	Gemcitabine-PEG-PLGA	In vitro: human lung cancer cell lines (A549)	[74]
Aptamer AS1411	Methotrexate-UnTHCPSi-PEI	In vitro: human breast adenocarcinoma cell lines (MDA-MB-231)	[75]
Aptamer AS1411	Docetaxel-mannitol-PLGA-TPGS	In vitro: human cervical carcinoma cell lines (HeLa) In vivo: cell lines HeLaxenograft	[76]
Aptamer AS1411	Doxorubicin-polymersome	In vitro: human breast adenocarcinoma cell lines (MCF-7) In vivo: cell lines MCF-7 xenograft	[77]
Galactose	Doxorubicin-LPL	In vitro: human liver cancer cell lines (SK-HEP-1) In vivo: cell lines SK-HEP-1 orthotopicxenograft	[78]
Galactose	5-Fluorouracil-pectin	In vitro: human hepatocellular carcinoma cell lines (HepG2)	[79]
Galactosamine	Paclitaxel-γ-PGA-PLA	In vitro: cell lines HepG2	[80]
Galactose	Doxorubicin solid lipid NP	In vitro: human lung cancer cell lines (A549)	[81]
EGF	Gemcitabine-stearoyl	In vitro: human breast adenocarcinoma cell lines (MDA-MB-468, MDA-MB-231, and MCF-7) In vivo: cell lines MDA-MB-468 xenograft Ex vivo: MDA-MB-468 tumor	[82]
EGa1	Doxorubicin-micelle	In vitro: human mouth squamous cell carcinoma cell lines UM-SCC 14 C In vivo: cell lines UM-SCC 14 C xenograft	[83]

peptide receptor are more sensitive to the lethal effects of a medication when it is delivered via a targeted NP than when it is delivered via a non-targeted nanoparticle (mean IC50: 35.53 ng/mL and 142.23 ng/mL). This is shown by contrasting the average IC50 values of the two nanoparticle kinds. By attaching the doxorubicin-loaded PLGA-PEG NPs to the NR7-peptide, we were able to selectively target the epidermal growth factor receptor (EGFR) found on cancer cells and deliver the medicine to them [236]. It is well established that the epidermal growth factor receptor (EGFR) overexpression is a hallmark of several malignancies, including non-small-cell lung, head and neck, kidney, ovarian, and breast cancers [237,238]. Activating this receptor promotes cancer survival and metastasis by increasing cell proliferation, inhibiting apoptosis, triggering angiogenesis, and reducing apoptosis. Hence, it is thought that inhibiting the activity of this receptor can enhance cancer treatment. Compared to non-targeted NPs, NR7-peptide-conjugated PLGA-PEG NPs were more effective in killing human ovarian cancer cells (SKOV3) [239].

One study found that an H2009.1 peptide-conjugated liposome could not improve the efficacy of doxorubicin when delivered to cancer cells expressing the integrin v6 receptor, despite the majority of studies showing promising results when using peptide- or protein-conjugated NPs to target cancer cells. The liposome platform blocked the targeted ligand's ability to attach to the cancer cell surface receptor, leading to inadequate drug accumulation in the malignant cells [240]. Table 3 below explains the NPS and its use in the respective area.

Clinical studies for another liposome, LEP-ETU, are now being conducted at the phase 1 level (NCT00080418). To combat ovarian, breast, and lung cancers, researchers created LEP-ETU, a liposome made of DOPC (1, 2-dioleoyl-sn-glycerol-3-phosphocholine2-dioleoyl-sn-glycerol-3-phosphocholine), cholesterol, and cardiolipin that incorporates paclitaxel [241]. Moreover, preliminary clinical studies (NCT00765973) have started to examine the effectiveness and security of topotecan liposomes supplied intravenously (TLI). While the clinical testing phase for these four drugs is over, more information has yet to be available to the general public. Clinical studies for LiPlaCis, INX-0076, and TLD-1 are still being conducted. INX-0076, a liposomal form of topotecan, is intended for use against solid, metastatic tumors. To treat patients with advanced solid tumors, the liposomal formulation LiPlaCis was created. Cisplatin and lipids, whose breakdown characteristics are regulated by the sPLA2 enzyme, are part of a release mechanism triggered by tumors [242]. Those with advanced solid tumors may benefit from TLD-1, a new liposome containing doxorubicin [243].

6. Challenges and future direction

There are still several issues in making nano drugs accessible to the general population despite these advancements. The main problem is that people must know how NPs interact with biomolecules. For many pharmaceutical firms, maintaining a consistent method for creating NPs that have an extended impact on cancer cells is risky. Drug manufacturers often discontinue producing their goods (e.g., DepoCyt). Several companies claim that technological issues are to blame for the delay. Before researchers and pharmaceutical firms can effectively promote cancer treatment, they must solve several problems. The FDA approved many nanoformulations, which were removed from the market. Feridex I.V. Lumirem, Resovist, and GastroMARK [244,245]. The application and sale of the findings of this study are fraught with issues. Several things might need to be corrected and cause the treatment to be delayed. Several of the problems are explored in this article.

Understanding what cancer nanomedicine can and cannot achieve has advanced significantly. Thorough patient selection is required to identify the individuals who would benefit most from a specific nano therapy due to the complexity and diversity of malignancies. These specialized medications are being created and given the green light for usage in patient populations that biomarkers can recognize. When therapeutic nanoparticles intended to treat solid tumors are administered to the body, a phenomenon known as EPR occurs [246]. This is assumed to be a result of the tumor's leaky blood arteries and inadequate lymphatic drainage. This interpretation of EPR, however, may be oversimplified because the effect can be influenced by a variety of biological processes, including interactions between NPs and proteins, blood flow, extravasation into and interaction with the perivascular TME, tumor tissue penetration, and internalization of tumor cells. These biological processes are all involved in the systemic delivery of NPs. The EPR effect and therapeutic results may thus be impacted by NP parameters like size, geometry, surface features, elasticity, stiffness, porosity, composition, and targeted ligand. It's crucial to keep in mind that although we've learned a lot about how NPs act in real life (in vivo), most of what we know is based on data from animal models, and the ramifications of this information on how NPs function in humans are still largely unknown [247].

Lipid-based carriers can cure a broad range of diseases. The number of formulations undergoing preclinical testing does not reflect the number of effective medications approved for sale. This shows that there are still many challenges and barriers to overcome in transferring these NPs from animals to people. To increase the stability of NPs and stop drug leakage, lipid patterns have been created that ionically bind the medicine within the capsule. It has been proven that ionizing lipids, such as DOP-DEDA, are the most effective at protecting genes. The drugs are packed tightly because cholesterol is necessary to stabilize liposomal structures. As their surfaces have been modified with PEG-lipids, LNPs are stable under physiologic conditions and during systemic circulation. This makes it difficult for the reticuloendothelial system to find them.

Nevertheless, it has been shown that when higher doses are given, the therapeutic effectiveness is reduced, and adverse consequences happen. This is because, after the first dose, anti-PEG antibodies start to build up. Thus, it is essential to find PEG substitutes so that injections may be given frequently. Long-circulating LNPs must reach the tissues, cells, or organs where they are to be used before piercing the cell membranes and releasing their payload. LNPs belong to this category because they are intelligent materials with unique ligands that degrade in reaction to variations in temperature, pH, reduction, or oxidation.

Targeted LNP binding to specific cells is still challenging. For example, the spleen and lymph nodes, which house immune cells that generate antibodies and eliminate cancer cells, are unsuitable delivery sites for a nucleic acid vaccine. Migrating nucleic acids from the puncture site to lymphocytes in the lymph nodes or spleen is the most effective way to generate antigen-specific cytotoxic T lymphocytes or long-lived antibodies. These methods must cross lymph node barrier cells and reach the proper lymph nodes to reach immune cells. After the drugs have entered the body, they must be controlled in their delivery to the abnormal cells. These technologies have yet to be the intended results, which help cells receive, internalize, and release their payload. The commercial success of LNPs with specific ligands has yet to be discovered. As a result, it is likely that clinical trials will soon start using various cell-type-specific ligands and stimulating agents to assess the effectiveness of modified LNPs against a range of diseases. In this field, adjuvants may boost a drug's efficacy or control the immune system's activity. It is also challenging to manufacture LNPs on a large scale. The most trustworthy LNP production methods now available are microfluidics-based, but they are limited in their ability to create LNPs with a wide range of relevant properties.

Due to the lack of complexity in biological tissues and the inability to regulate fluid flow, conventional in vitro models using cells expanded in multiwall plates may not accurately replicate the complex interaction of NPs with physiological barriers. By adopting biomimetic "organ/tumor-on-a-chip" techniques, conventional in vitro models may be enhanced [248,249]. Suppose tumor-like spheroids are inserted into a microfluidic channel. In that case, it is expected that the impact of interstitial flow, cell attachment, and particle size on NP accumulation and diffusion will be better understood. Comparing NP behaviors in such chip systems to those in animal models may be helpful in understanding the future of

these biomimetic microdevices.

Animal models must be used to figure out how well NPs work in living organisms (in vivo) and how safe they are. Many species, including humans, have shown that pharmacokinetic (PK) scaling works for several Nanotherapeutics. However, it is well known that the effects seen in preclinical research are different from those seen in clinical trials [250,251]. This is primarily a result of the lack of suitable tumor models. We have access to a broad range of animal models, including patient-derived xenografts (PDXs), subcutaneous and orthotropic xenografts produced from cell lines, and mice genetically altered. No animal model can accurately replicate every aspect of cancer. They exhibit more consistency in their responses than those with the disease. Because metastases are a leading cause of cancer-related mortality, human tumor migration models will help compare EPR and NP penetrating and placement in metastatic tissues to that of primary tumors. High-fidelity PDXs, humanized animal studies [252], and (GEMMs) genetically engineered mouse models with aggressive tumor growth are just a few examples of animal studies that could closely match the diversity and anatomical histology of malignant tumors and have the potential to improve the translation of Nano-therapeutics [253] significantly.

7. Conclusion

Conclusively, the overall study suggests that compared to conventional chemotherapy methods, nanoparticles in anticancer therapy are rapidly developing fields that offer several benefits. To ensure that the drugs are delivered directly to the tumor cells with the least harm to healthy cells, nanoparticles can provide targeted and sustained release by encapsulating the drugs. The choice of nanoparticle type is critical to attaining good treatment outcomes, as various nanoparticles have diverse features, including size, shape, and surface charge. Many forms of nanoparticles, including liposomes, dendrimers, and quantum dots, have demonstrated substantial potential for improving the effectiveness of cancer treatment. To further increase the precision of nanoparticle drug delivery, active and passive targeting mechanisms have been established. As this review has shown, nanoparticles have the potential for the development of safer and more productive cancer therapies, such as co-delivery of combinational medications, stimuli-responsive drug release, and targeted drug delivery. These capacities could facilitate long-term outlooks and the development of innovative cancer treatment strategies. Studies conducted in vitro and in vivo have established the safety and effectiveness of nanoparticle-based therapeutics, and showcased some superior efficacy than conventional chemotherapy. To enhance these treatments, further study is needed, including creating more effective targeting mechanisms and advancements in nanoparticle designs. Though not all of these intelligent nanoparticles have been effective in their clinical translation, several innovative materials are now being created that show great potential and are encouraging new treatment options. Despite these obstacles, nanoparticles can potentially transform cancer treatment by providing a more focused and practical approach in the biomedical field.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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