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REVIEW ARTICLE

Nanoparticles, Aptamers, and Aptamer-Conjugated Nanoparticles in Cancer Therapy

Muhamad Muhamad AlKRIZ[*°], Dima JOUJEH[**]

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SUMMARY

Cancer represents one of the main causes of death around the world, causing about 10 million deaths in the year 2020. Large progress has been made in the discovery of targeted therapy for cancer in recent years. Targeted therapy is a branch of cancer treatment that targets a specific site, without affecting the surroundings. The current review focused on recent achievements in the field of targeted anti-cancer drug delivery based on aptamers, nanoparticles, and aptamer-conjugated nanoparticles. It included a comprehensive survey of almost all recent studies published on this topic and comprehensively discussed the properties, advantages, and disadvantages of using these formulations as delivery vehicles in cancer therapy. We also provided examples of nanoparticles, aptamers targeting cancer biomarkers, aptamer-drug conjugates, and aptamer-conjugated nanoparticles, employed in targeted cancer therapies, and discussed the cytotoxicity of these formulations on cancer and non-cancer cell lines. The factors that can trigger nanoparticles for optimal drug release were also discussed. We hope that this review will provide additional information that will facilitate advanced applications of nanoparticle/ aptamer-based drug delivery systems for cancer therapy.

Key Words: *Cancer, biomarkers, nanoparticles, aptamer, drug delivery, aptamer-conjugated nanoparticles.*

Kanser Tedavisinde Nanopartiküller, Aptamerler ve Aptamer-Konjuge Nanopartiküller

ÖZ

Kanser, 2020 yılında yaklaşık 10 milyon ölüme neden olan tüm dünyada ölümlerin başlıca nedenlerinden biridir. Son yıllarda kanser için hedeflendirilmiş tedavinin keşfinde büyük ilerleme kaydedilmiştir. Hedeflendirilmiş tedavi, kanser tedavisinin bir parçasıdır ve çevre dokuları etkilemeden spesifik bir alanı hedefler. Mevcut derleme, aptamer, nanopartiküller ve aptamer-konjuge edilmiş nanopartiküller ile ilgili hedeflendirilmiş anti-kanser ilaç tedavisi alanındaki son gelişmelere odaklanmıştır. Bu makalede konuyla ilgili son yıllarda yayınlanan neredeyse tüm çalışmaların kapsamlı bir incelenmesi ve kanser tedavisinde bu formülasyonların tedavi aracı olarak kullanımının özellikleri, avantajları ve dezavantajları kapsamlı olarak tartışılmıştır. Hedeflendirilmiş kanser tedavilerinde kullanılan nanopartiküller, kanser biyobelirteçlerini hedef alan aptamerler, aptamer ilaç konjugatları ve aptamer-konjugat nanoparküllerin örnekleri de sunulmuş ve bu formülasyonların kanser ve kanser olmayan hücre hatları üzerindeki sitotoksisitesi tartışılmıştır. İlaçların optimum şekilde salım yapması için nanopartikülleri tetikleyebilecek faktörler de tartışılmıştır. Bu derlemenin, kanser tedavisi için nanopartikül/aptamer temelli ilaç taşıyıcı sistemlerinin gelişmiş uygulamalarını kolaylaştıracak ilave bilgiler sağlayacağını umuyoruz.

Anahtar Kelimeler: *Kanser, biyobelirteçler, nanopartiküller, aptamer, ilaç taşıyıcı sistem, aptamer-konjuge nanopartiküller.*

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[*] ORCID: 0009-0009-7076-3074, Biotechnology engineering, Faculty of Technical engineering, University of Aleppo, Syria.
[**] ORCID: 0000-0001-8240-9886, Biotechnology engineering, Faculty of Technical engineering, University of Aleppo, Syria.

[°] Corresponding Author; Muhamad Muhamad Alkriz:
Email Address: muhamadalkriz@gmail.com.

INTRODUCTION

Cancer represents one of the main causes of death around the world, causing about 10 million deaths in the year 2020. One of the hallmarks of this disease is the rapid creation of abnormal cells that grow outside their usual boundaries, which may later go on to invade neighboring parts of the body and spread to other organs. The latter process is referred to as "metastasis" (WHO, 2022). Anti-cancer drugs can be synthesized chemically, or derived from natural sources (Tewari et al., 2019). However, more than 60% of contemporary anti-cancer drugs, in all their forms, come from natural sources (Joujeh and Joujeh, 2023).

Large progress has been made in the discovery of targeted therapy for cancer in recent years. But, even for the most impactful drugs that have been accepted, acquired and innate resistance mechanisms are common (Ward et al., 2021).

Current cancer therapies, including radiotherapy and chemotherapy, often lack specificity for tumor cells, leading to severe toxic effects in cancer patients undergoing the treatments (Liu et al., 2014). Among these include peripheral neuropathy, hair loss, diarrhea, and loss of appetite (Awasthi et al., 2018).

Targeted therapy is a branch of cancer treatment that targets a specific site, without affecting the surroundings. This significantly increases the specificity and reduces toxic effects (Pucci et al., 2019). Available drug delivery systems (DDS) include liposomes, micelles, vesicles, and nanospheres that act to transport anticancer agents into the body (Ghasemi et al., 2022). The combination of chemotherapy and nanotechnology can offer several advantages such as improved drug bioavailability and prolonged release of the chemotherapeutic agent. To achieve active targeting, biomolecules such as peptides, antibodies, and aptamers can be conjugated to nanoparticles (Kadkhoda et al., 2022). This combination could provide a promising candidate with the potential for an effective and safe delivery option in oncotherapy (Sheikh et al., 2022).

The current review focused on recent achievements in the field of targeted DDS based on aptamers, nanoparticles, and aptamer-conjugated nanoparticles, and comprehensively discussed the properties, advantages, and disadvantages of using these formulations as delivery vehicles in cancer therapy.

METHODOLOGY

Data was obtained from extensive literature searches using internet databases, mainly PubMed and google scholar, using the keywords 'aptamers', 'nanoparticles', 'drug delivery', 'aptamer- conjugated nanoparticles', 'cancer diagnosis', and 'cancer therapy'. Online search was mainly devoted to publications written in English.

Nanoparticles And Cancer

Nanoparticles (NPs) are materials ranging in size from 1 to 100 nm. They assume various forms, including nanoparticles, nanotubes, nanofilms, and bulk nanomaterials like dendritic structures. These entities possess unique properties, such as novel reactivity, and mechanical, electrical, and magnetic properties (Yetisgin, et al., 2020; Shrestha et al., 2020). They have unique physico-chemical properties, such as biocompatibility, biodegradability, and environmental sustainability (Hazra et al., 2023).

Being smaller than cells, nanoparticles can cross biological barriers to deliver the drug to the targeted site, increasing drug durability in the bloodstream and enabling targeted drug delivery (Aghebati-Maleki et al., 2019).

Nanotechnology offers new frontiers for cancer therapy, specifically through Nano Drug Delivery Systems (Ahmed et al.,2022). Loading oncology drugs inside the carrier or adsorbing them on the carrier surface helps to protect the drugs from premature elimination and enhance the solubility of insoluble drugs (Ahmed et al., 2022). There are various types of targeted drug delivery systems using nanoparticles (Figure 1). NPs can be categorized into mesoporous silica, liposomal, polymer, metal, carbon, and protein-based NPs (Herdiana et al., 2021). Some of the nanoparticles employed in targeted cancer therapies are listed in Table 1.

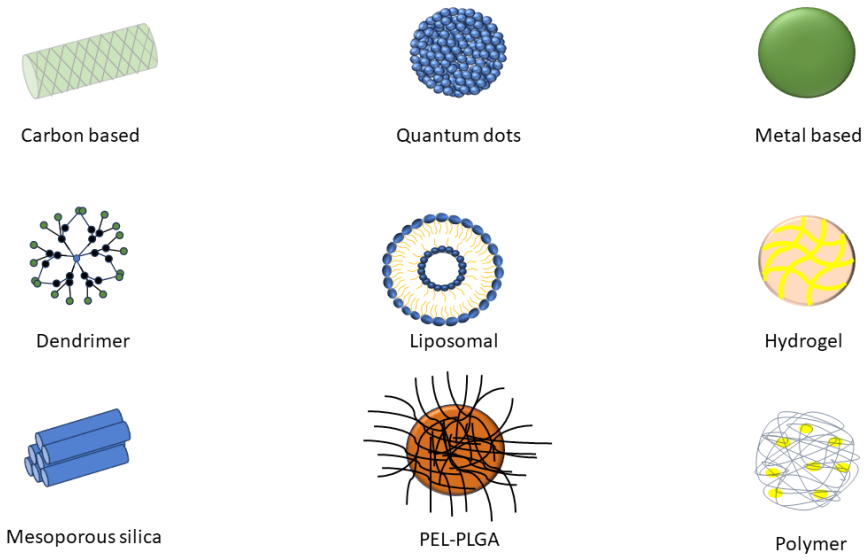

Figure 1. Types of nanoparticles for targeted drug delivery systems

Table 1. Some of the nanoparticles employed in targeted cancer therapies

Nanoparticle	Target Cells	Targeted Cancer	Loaded drug / Therapy	Ref
GNP	HeLa	Cervical Cancer	DOX	(Bansal et al., 2023)
PCL-Chitosan	HCT 116	Not specified	Berberine, Curcumin	(Ghaffarzadegan et al., 2023)
NC-NP	4T1	Not specified	DACHPt	(Xiang et al., 2023)
Chitosan-based microgels	4T1	Not specified	piperine	(Wang et al., 2023)
MSLN	MDA-MB-231	Breast cancer	ATS, VIN	(Shinde et al., 2023)
PMNP-D	CAFs	ACC	DOX	(Liu et al., 2023)
Nanomicelles (PLGA,PCL,PSt)	4T1, SPC-A1 MHCC-97H,	Not specified	PTX	(Miao et al., 2023)
D-g-PAA-GNP	MDA-MB-231, MCF10A	TNBC	Photodynamic therapy	(Warren et al., 2023)
CS- NZIF-8	MCF-7	breast cancer	curcumin, 5-FU	(Radhakrishnan et al., 2023)
BPCA1-BPCA4	MCF-7	breast cancer	DOX	(Du et al., 2023)
QD@Ca	4T1, MDA-MB-231	breast cancer	Sonodynamic therapy with DOX	(Cai et al., 2023)
Tc -HAS	MCF-7, 4T1	breast cancer	Methotrexate (MTX) Trastuzumab (TRZ)	(Ekinci et al., 2023)
(TB) (PCL-PEG-PCL)	HCT-119, HT-29	Colorectal cancer	PGZ, CAP	(Pouya et al., 2023)
CDs-PEG4-β-Cdx	tumors overexpressing PDE-5	Not specified	Sildenafil	(Mauro et al., 2023)

(GNPs) gold nanoparticles, (DOX) doxorubicin, (PCL) Polycaprolactone, (HCT116) human colorectal carcinoma cells, (NC-NP) Norcantharidin-Platinum Codelivery Nanoparticles, (4T1) Mouse breast cancer cell line, (DACHPt) 1,2-diamino cyclohexane-platinum (II) a parent drug of oxaliplatin, (PLGA) poly (lactic-co-glycolic acid), (MSLNs) Mannose-conjugated Solid Lipid Nanoparticles, (MDA-MB-231) human breast cancer cell line, (ATS) Atorvastatin Calcium, (VIN) Vinpocetine, (PMNPs-D) CAF-associated ITGB1-inactivating peptide-enriched membrane nano delivery system, (CAFs) Cancer-associated fibroblasts, (ACC) adenoid cystic carcinoma, (PSt) polystyrene, (SPC-A1) human lung carcinoma cell line, (MHCC-97H) Human hepatocellular carcinoma cell line, (PTX) Paclitaxel, D-g-PAA-GNP) Dextran-grafted-polyacrylamide encapsulated with gold nanoparticles, (TNBC) Triple Negative Breast Cancer, (MCF-7) human breast cancer cell line, (5-FU) 5-Fluorouracil, (BPCA1-BPCA4) Biotin-linked Amphiphilic Calix arene-based Supramolecular Micelles, (QD@Ca) Quantum Dots @ Calcium, (Tc) Technetium-99m, (MTX) Methotrexate, (TRZ) Trastuzumab, (HSA), Human Serum Albumin, (CAP) Capecitabine, (PGZ) pioglitazone hydrochloride, (TB) triblock (CDs-PEG4-β-Cdx) β-Cyclodextrin-decorated sulfur-doped carbon nanodots.

Aptamers

Aptamers are short, single-stranded oligonucleotides (Zhang et al., 2019). They are classified as DNA or RNA aptamers or peptide aptamers (Odeh et al., 2019). The most important merits of using aptamers are that there are no limitations on their targets, their ease of generation, low production cost, reversible folding properties, and low immunogenicity (Kim et al., 2016). Aptamers can target a wide range of entities, from small molecules to biomacromolecules, infected cells, stem cells, and cancer cells (Zhu and Chen 2018). Aptamers mimic antibodies by binding to a specific target molecule (Byun et al., 2021) with high affinity and specificity by folding into tertiary structures (Zhang, et al., 2019). However, unlike antibodies, aptamers are more stable, especially after chemical modifications (Subjakova et al., 2021). Therefore, they can be synthesized in large quantities and stored without or with minimal loss in activity (Odeh al., 2019). They can withstand temperatures of up to 95°C without losing their structure upon cooling. They also can be stored in a freezer (-18°C) under dry conditions for up to a year (Subjakova et al., 2021). They are chemically synthesized under in vitro conditions, avoiding the use of experimental animals, and offer advantages such as relative resistance to changes in pH, temperature, and ionic concentrations, as well as cost-effective production (Reid et al., 2020).

Selex Technique

Even though some aptamers exist naturally, most of them are generated in vitro by selecting them from a large random sequence pool (Qian et al., 2021). The procedure for *in vitro* aptamer synthesis is known as the "Systematic Evolution of Ligands by Exponential Enrichment (SELEX)" (Srivastava et al., 2021). SELEX is a comprehensive, multidisciplinary project involving various fields, including molecular biology, analytical chemistry, bioinformatics, materials chemistry, and nucleic acid chemistry.

SELEX is used to isolate aptamers with high affinity and specificity for a variety of target molecules from a carefully designed oligonucleotide library (Qi et al., 2022). To achieve this, target-related sequences were iteratively selected and amplified to preferentially enrich those sequences with the highest affinity for the target (**Figure 2**). Traditionally, after 10 to 15 iterations, one or more aptamers can be identified. This process can take several months to complete (Szeto et al., 2013). In recent decades, the SELEX protocol has been further innovated and developed, leading to the emergence of new SELEX technologies to simplify the procedure and expand the variety of aptamers, such as Graphene oxide (GO)-SELEX, Capillary electrophoresis (CE)-SELEX, Cell-SELEX, and Fluorescence-activated cell sorting (FACS)-SELEX (Lyu et al., 2021).

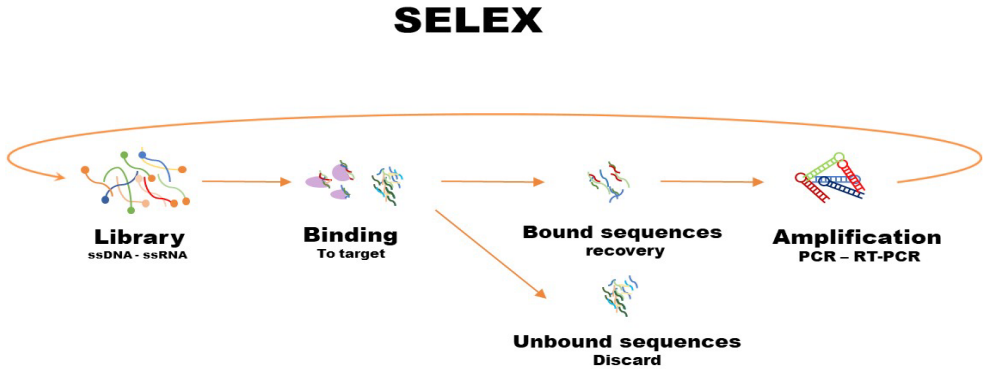

Figure 2. Schematic representation of in-vitro SELEX procedure

Aptamers and Cancer

Aptamers' specificity has been harnessed in targeting cancer cells. As mentioned earlier, aptamers are novel oligonucleotides that recognize and bind to their cognate targets, including tumor surface receptors (Zhu et al., 2014). Aptamers can act as antagonists, inhibiting the interaction of tumor-related targets (proteins or receptor-ligands), or as agonists, activating the function of anti-cancer target receptors, contributing to potential anti-tumor therapeutic strategies (Li et al., 2021). Some *in vivo* experiments indicate that aptamers can inhibit the growth of tumors overexpressing receptor-related targets, positioning them as promising anti-tumor therapeutic agents (Wang and Li, 2011). Cancer biomarkers are molecules that indicate abnormalities in cancer and play an important role in many biological processes, including cell migration, cell-cell interactions, signal transduction, and cell proliferation (Sawyers., 2008).

Numerous biomarkers have been identified as key players in different types of cancer. For example, mucin 1 (MUC1) and nucleolin are frequently overexpressed in breast cancer cells (Yang et al., 2023). Similarly, prostate-specific membrane antigen (PSMA), a carboxypeptidase, is known to be upregulated at various stages of prostate cancer development (Cruz-Hernández et al., 2022). Another important biomarker is the human epidermal growth factor receptor 2 (ErbB-2/HER2), a receptor tyrosine kinase, which is commonly overexpressed in various human cancers, such as gastric and breast tumors (Kara et al., 2023). EpCAM, a tumor-associated antigen, is highly expressed in common epithelial cancers and their tumor-initiating cells, making it a crucial focus of research (Holz et al., 2023). Additionally, PTK7-receptor is another biomarker known to be overexpressed in various types of tumors (Sicco et al., 2021). Aptamer has proven to be sensitive in detecting the overexpressed biomarker on the surface of cancer cells and has emerged as a new targeting material due to its high affinity for target molecules. It recognizes and binds to its corresponding target by spontaneously forming a three-dimensional (3D) structure (Figure 3), aiming to improve therapeutic effects and minimize toxicity to non-cancerous cells (Kim et al., 2018). Table 2 displays some of the aptamers targeting biomarkers that have been studied for the diagnosis and treatment of cancer.

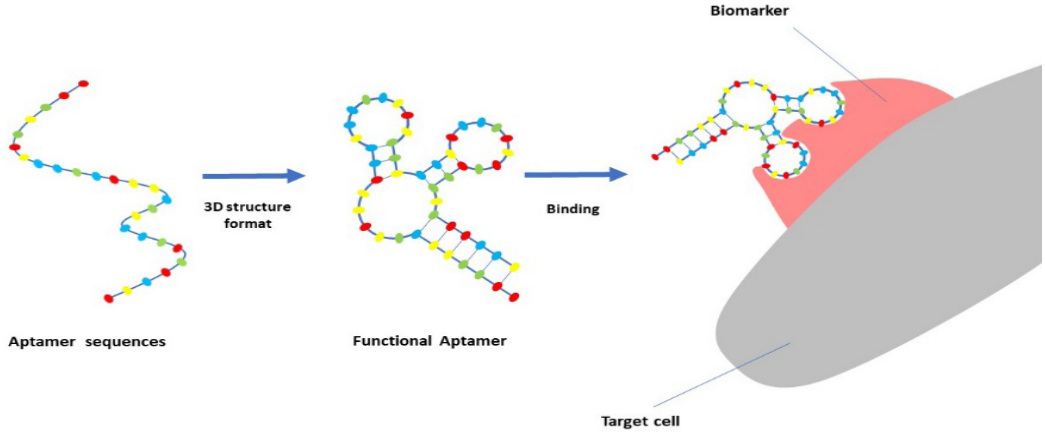

Figure 3. Schematic diagram of aptamer targeting cancer biomarker

Table 2. Aptamers targeting cancer biomarkers

Aptamer	Target	Target cells	Cancer type	Ref
AB3 5'-TGCGTGTGTAGTGTGTCT-GTTGTTTGTATTGTTGTCTATCCTCT-TAGGGATTTGGGCGG-3'	OFA/RP	hematologic tumor cells	Hematologic malignancies cancer	(Rus et al.,2023)
S1–4	(ER+)	MCF-7	breast cancers	(Cong et al.,2023)
AS1411 5'-GGTGGTGGTGGTTGTGGTGGTG-GTGG-3'	nucleolin	MCF-7	breast, cervical, and colon cancer	(Gupta et al.,2023)
W3 AGCAGCGTGGAGGATAGGGGTC-GGAGTGGGTGGTTATGATTG-GCTCTTCTGCGCTGC	CTCs and exosomes derived from CRC cells		colorectal cancer	(Lu et al.,2023)
A2 CACCACGCGAATGCTATCGGGGCTA-AGTATCAAAATGAGC	β1-integrin	KYSE410	ESCC	(Zhang et al.,2022)
yly12 AGGATAGGGGGTAGCTCGGTC-GTGTTTTTGGGTTGTTTGGTGG-GTCTTCTG	L1CAM	LoVo, PC3	colon/prostate cancer	(Long et al.,2023)
GreenB1 5'-FAM-ATCCAGAGTGACGCAGCAG-GTGGAAGGGGTAACTACGTGGG-GAGGTGGTAGGGGTGGGTGGACAC-GGTGGCTTAGT-3'	β1-integrin,	MCF-7, MDA-MB-231, and MDA-MB-436	triple-negative breast cancer	(Pleiko et al.,2023)

(OFA) Oncofetal antigen, (RP)immature laminin receptor protein, (HR+) Hormone Receptor-Positive, (CTCs) Circulating tumor cells, (ESCC) Esophageal squamous cell carcinoma, (KYSE410) derived from the poorly differentiated invasive esophageal squamous cell carcinoma, (LoVo) colon cancer, (PC3) prostate cancer, (L1CAM) L1 cell adhesion molecule, (CRC) Colorectal cancer

Chemotherapy is the most common cancer treatment. However, it still has many side effects. Because most drugs kill cancer cells and normal cells, they lack selectivity (Fan et al., 2023).

Aptamer, with its excellent specificity, has rapidly become a new type of targeted ligand used in drug delivery. Many aptamer-mediated DDS have been developed, including drug-aptamer conjugates, aptamer-siRNA, and aptamer-functionalized nanoparticle systems for effective cancer treatment (He et al., 2023). Aptamer has been used as a drug carrier that can conjugate with chemotherapeutic agents or potent toxins and deliver them precisely into tumors by targeting specific cell surface antigens, significantly improving the therapeutic effectiveness of drugs in cancer treatment (Yang et al., 2021).

Notably, the aptamer/drug ratio plays a crucial role in achieving optimal therapeutic efficacy (Gao et al., 2022). The aptamer-drug conjugate typically consists of three molecular components: the aptamer (ligand), linker, and drug. Aptamer serves as a ligand for targeting disease sites and guiding the delivery of therapeutic agents that modulate the biological function of the target biomarker (Kim et al., 2021). Table 3 displays recent research on targeted cancer therapy using aptamer-drug conjugates.

Table 3. Aptamer-drug conjugates for cancer therapy

Aptamer	Target	Cell line	Drugs loaded	Cancer type	Ref
BGA	nucleolin	MCF-7	DM1	Breast cancer	(Jo et al., 2023)
PTK7 AP	PTK7	5637	GEM	bladder cancer	(Xiang et al., 2022)
Sgc8	PTK7	A20	dasatinib	Lymphoma	(Sicco et al., 2023)
E3	(Tf 1).	LNCaP, DU145, PC3, 22RV1	E (MMAE) F (MMAF)	prostate cancer	(Song et al., 2023)
CD71/CD44 dual-aptamer	CD71/CD44	TCCSUP, UM-UC-3, EJ, and T24	GEM	bladder cancer	(Liu et al., 2023)
CD133 RNA	CD133	BAKP POT	trametinib mebendazole	melanoma cancer	(Haribabu et al., 2022)
anti-CD20	CD20	WM266-4, A375	Adriamycin	Melanoma cancer	(Chen et al., 2023)
AS1411, FOXM1	----	4T1	epirubicin	Breast cancer	Moradi et al., 2023)
EpCAM AP	EpCAM	Hep3B, Huh7	Dox	Hepatocellular carcinoma	(Zhou et al., 2022)
apHAT610	HAT1	A549, SW900, H1650	the aptamer is a potential drug	Lung cancer	(Klett-Mingo et al., 2022)

(GEM) Gemcitabine, (PTK7) protein tyrosine kinase 7, (A20) Mus musculus B lymphoma A20 cell line, (Tf 1) transferrin receptor 1, (MMAE) monomethyl auristatin E, (MMAF) monomethyl auristatin F, (WM266-4 and A375) are human melanoma cell lines, (EpCAM) Epithelial cell adhesion molecule, (Hep3B, Huh7) HCC cell lines, (HAT1) Histone acetyltransferase 1, (5637) human bladder cancer cells, (DM1) drug has synergistic interaction with TOP1 inhibitors.

Aptamers in Clinical Trials

After the discovery of aptamers, great efforts were made by researchers to achieve the clinical use of aptamers in treating diseases (Esawi et al., 2023). Many aptamers are currently at various stages in clinical trials. Figure 4 displays the number of Aptamer-based clinical trials by year, according to the official database of the US National Institutes of Health.

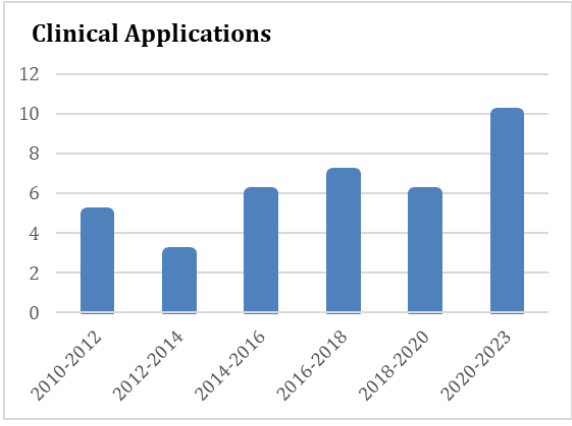

Figure 4. Number of aptamer-based clinical trials by year (www.clinicaltrials.gov)

Macugen® (pegaptanib) was the first aptamer-based drug approved by the US Food and Drug Administration (FDA) in December 2004 (Liu et al., 2022). Pegaptanib targets vascular endothelial growth factor (VEGF) for the treatment of neovascular age-related macular degeneration. It was also the first anti-angiogenic agent approved for this common eye disorder (Fine et al., 2005). VEGF plays an important role in tumors. Therefore, it was thought that Macugen might also have anti-cancer properties as well. Unfortunately, preclinical studies failed to support this hypothesis, so the drug has not been tested in clinical trials for oncology applications (Morita et al., 2018). To date, only a few therapeutic aptamers have progressed successfully into clinical trials for oncology (Table 4), but no aptamer has been approved by the FDA for cancer treatment (Shigdar et al., 2021).

- AS1411

The nucleolin-targeting DNA aptamer AS1411 is advanced in cancer therapy with great potential for clinical use due to its safety profile and ability to in-

duce strong response in a patient with intractable tumors (Yazdian-Robat et al., 2020). The unique G-rich quadruplex structure and pegylation support the pharmacokinetic (PK) profile of AS1411, resulting in nuclease evasion and an extended half-life (Morita et al., 2018).

Two clinical trials on AS1411 have been conducted to evaluate its efficacy in advanced solid tumors (NCT00881244) and renal cell carcinoma (RCC) (NCT00740441). Despite the trial (NCT00881244) being completed in 2007, no reports have been published about the outcomes. In a phase II trial (NCT00740441), the drug was found to have minimal activity in unselected patients with metastatic RCC (Rosenberg et al., 2014).

AS1411 is also being used in clinical trials to treat leukemia. A phase II clinical trial evaluated the efficacy of AS1411 in combination with cytarabine in patients with acute myeloid leukemia (AML), the results demonstrated that the combination therapy was superior to cytarabine alone (Stuart et al., 2009). Other phase II clinical trials (NCT00512083 and NCT01034410) aimed to assess the efficacy of AS1411 combined with cytarabine for the treatment of AML, but the results have not been published yet.

- NOX-A12:

NOX-A12 is an RNA-aptamer that targets CXCL12. NOX-A12 demonstrated improved overall response rates in chronic lymphocytic leukemia (CLL) patients in a phase I/II trial (NCT01486797) when combined with bendamustine and rituximab chemotherapy (Steurer et al., 2019). Clinical studies (NCT00976378 and NCT01194934) determined the safety profile of NOX-A12 in healthy volunteers. A second phase I clinical trial (NCT01194934) demonstrated that NOX-A12 is safe, well-tolerated, and effective in vivo by counteracting CXCL12 signaling (Vater et al., 2013).

Through a Phase I/II study (NCT03168139) in patients with metastatic microsatellite-stable colorectal and pancreatic cancer, with impaired immune systems, the combination of NOX-A12 and pembrolizumab was found to induce immune responses, stable disease in 25% of patients, and prolonged time on treatment (Halama et al., 2019).

A phase 2 study (NCT01521533) compared a single intravenous dose of NOX-A12 alone versus a combination with bortezomib and dexamethasone (VD) in previously treated multiple myeloma patients. The results indicated that NOX-A12 increased the efficacy of VD treatment without increasing treatment toxicity (Ludwig et al., 2017). Updated data from the expansion arm of the phase 1/2 GLORIA trial (NCT04121455) showed that the addition of NOX-A12 to standard-of-care radiotherapy and bevacizumab elicited a response when used as first-line treatment for patients with glioblastoma (Giordano et al., 2023).

- SGC8:

The Sgc8 single-stranded DNA aptamer (ssDNA) has been shown to accumulate more in PTK7-positive tumors and is currently under the early-phase I clinical trial (NCT03385148) to assess its diagnostic value in colorectal cancer.

- EYE001:

A phase I clinical trial (NCT00056199) aimed to test the ability of EYE001 to reduce retinal thickening, and improve vision in patients with Von Hippel-Lindau syndrome. Although this study was completed in 2005, no report of the results has been posted on (clinicaltrial.gov) or publicly published yet.

Table 4. Aptamers used in clinical trials for cancer diagnosis and therapy (www.clinicaltrials.gov)

Aptamer	Type	Study Phase	Primary Purpose	Cancer	Last Update	Clinical Trial ID
AS1411	DNA	Phase 1	Treatment	Solid Tumours	2009-04	NCT00881244
AS1411	DNA	Phase 2	Treatment	Renal Cell Carcinoma	2009-09	NCT00740441
AS1411	DNA	Phase 2	Treatment	Acute Myeloid Leukemia	2009-09	NCT00512083
AS1411	DNA	Phase 2	Treatment	Acute Myeloid Leukemia	2017-12	NCT01034410
NOX A12	RNA	Phase 2	Treatment	chronic lymphocytic leukemia (CLL)	2017-05	NCT01486797
NOX A12	RNA	Phase 1/2	Treatment	Metastatic Colorectal and Pancreatic Cancer	2020-07	NCT03168139
NOX A12	RNA	Phase 2	Treatment	Relapsed Multiple Myeloma	2015-10	NCT01521533
NOX A12	RNA	Phase 1/2	Treatment	Glioblastoma	2023-06	NCT04121455
Sgc8	ssDNA	Early Phase 1	Diagnostic	Colorectal cancer (CRC)	2011-02	NCT03385148
EYE001	RNA	Phase 1	Treatment	Retinal angioma	2008-03	NCT00056199

Aptamer-Conjugated Nanoparticles:

Nanotechnology-based drug delivery systems provide an advanced approach for precise and sustained drug delivery, ensuring optimal therapeutic outcomes over the desired timeframe and reducing the frequency of administration (Sheikh et al., 2022). A significant challenge in this field is to equip multifunctional polymeric nanoparticles with the ability to target specific molecules, evade the immune system, and control drug release to overcome biological barriers *in vivo* (Fang et al., 2020). Functionalizing nanoparticles using specific receptors has gained significant attention. Aptamers, known for their high specificity and affinity emerge as prime candidates for specific nanoparticle receptor functionalization (Kumar et al., 2023).

Although the aptamer can be directly conjugated to anticancer agents such as chemotherapeutic, the advantage of using nanoparticles is that they can deliver large quantities of drug payload or diverse treatments to cancer cells through delivery and recognition events (Fu et al., 2020). This combination is promising progress for targeted drug delivery (Gao et al., 2022). A schematic representation of aptamer-functionalized nanoparticles acting on a cancer cell is shown in Figure 5.

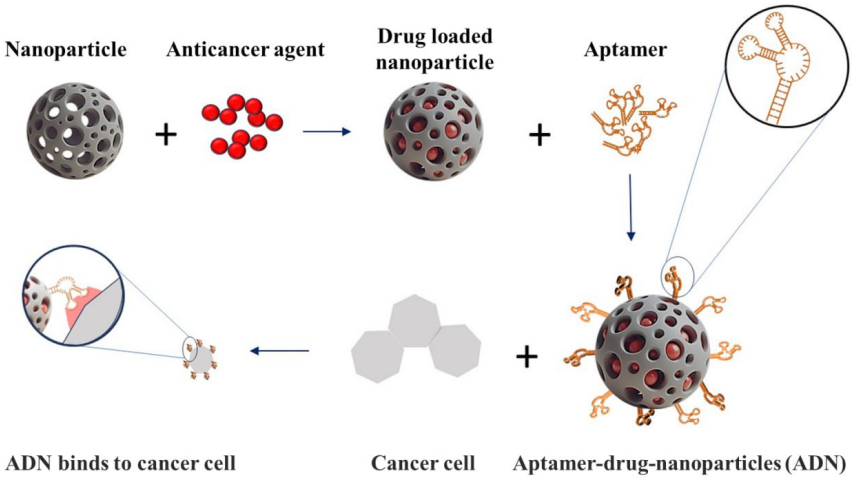

Figure 5. A schematic representation of aptamer-functionalized nanoparticles acting on a cancer cell

Recently, combinations of aptamers and nanoparticles have been widely used in the development of therapeutic platforms due to their unique potential in targeted drug delivery systems, diagnostics, and response monitoring (Khan et al. 2022). Some of the aptamer-NP structures used in anticancer drug delivery are listed in Table 5.

The concept of aptamer-conjugated nanoparticles was developed to overcome the drawbacks related to using each of them individually. To elucidate this idea, we compare three delivery systems developed to assess the effectiveness of Doxorubicin as a targeted treatment against MCF-7 cancer cells, including an aptamer-based delivery system, in which DOX was loaded between two complementary sequences of AS1411 (Rahimi et al., 2022), nanoparticle-based delivery system, in which DOX was loaded onto PEG-chitosan- mesoporous silica nanoparticles (MSN) (Moodley et al., 2020), and aptamer-conjugated nanoparticles- based delivery system, in which DOX was loaded into MSNs, chitosan was employed to cover the surface of MSNs, and AS1411 aptamers were electrostatically attached to the surface of the chitosan-coated MSNs (Khatam et al., 2021). By comparing the results of these reports (Figure 6), it can be observed that the aptamer-conjugated nanoparticles can combine the advantages of aptamer-drug conjugates and nanoparticle carriers, providing high target specificity, controlled release and increased toxicity to cancer cells while maintaining a high rate of viability for normal cells.

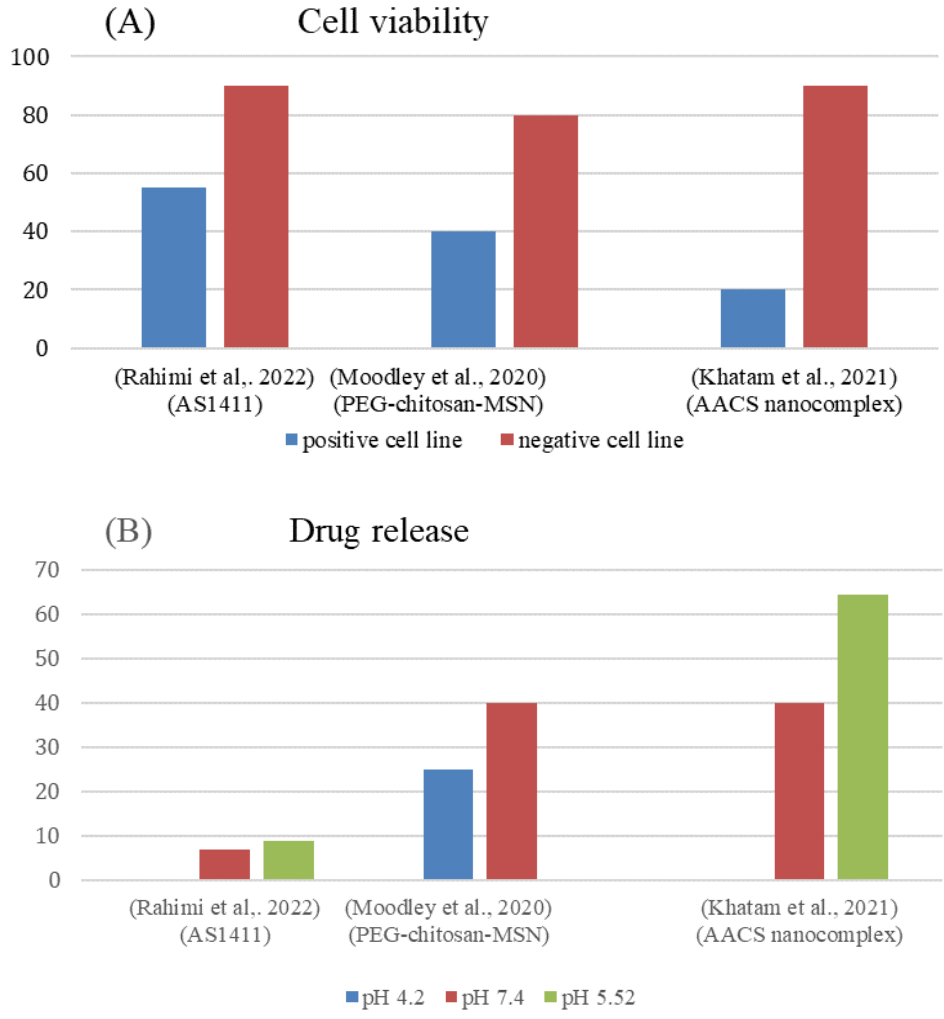

Figure 6. Comparison of cell viability (A) and drug release efficiency (B) between the results of previous reports

Table 5. Aptamer-NP formulations used for anti-cancer drug delivery

Aptamer	NPs	Drug	Target	Cell line	Cancer Type	Ref
Aptamer	CS/COQ	FU-5, GA	Not specified	MCF-7	Breast cancer	(Mazandarani et al., 2023)
MUC16 AP	MSNPs-PEG	SUN	mucin 16	OVCAR-3, SK-OV-3	Ovarian cancer	(Torabi et al., 2023)
AS1411 AP	CuFePBA@PEGMA	DOX	nucleolin	MCF-7 4T1	Breast cancer	(Chen et al., 2023)
	CoFePBA@PEGMA					
Sgc8c AP	mSiO2-Au	AZD5363	PTK-7	CCRF-CEM	T-ALL	(Yang et al., 2023)
AP613-1 AP	(H-MnO2)	SRF	GPC3	Huh7, HepG2	(HCC)	(Wang et al., 2023)
MUC1 AP	PEG-Au	PTX	mucin 1	MCF-7	Breast cancer	(Kadkhoda et al., 2022)
AS1411 AP	ICG, TOA	DOX	nucleolin	4T1	Breast cancer	(Li et al., 2023)
MUC1 AP	Fe3O4@GO@Ce6	PAC	mucin 1	MCF-7	Breast cancer	(Işıklan et al., 2022)
HB5 AP	cGO	Sili, DOX	HER2	MCF-10A, MCF-7, SK-BR-3	Breast cancer	(Shahidi et al., 2023)
AS1411 AP	CSSD	DOX	nucleolin	MDA-MB-231, 4T1	Breast cancer	(Yu et al., 2023)
AS1411 AP	PEG-b-PVGLIG-PLA	SN38	nucleolin	C26	Colon cancer	(Ramezani et al., 2020)
ΔPSap4#5 AP	PLGA	ABR	PSMA	LNCaP,22Rv1	Prostate cancer	(Al Hoque et al., 2023)
MUC1 AP	NHG-QDs	PTX/SO	mucin 1	MCF-7	Not specified	(Ranjbar-Navazi et al., 2021)
MUC-1 AP	nano barrel	PTX, DOX	mucin 1	MCF-7	Breast cancer	(Wang et al., 2023)
CD117 AP	PEG	Drn/Lut	Tf /CD117	HL60	Leukemia	(Zhu et al., 2023)

(CS/COQ) Chitosan and carbon quantum dot, (GA) *Ganoderic acid*, (MSNPs) Mesoporous silica nanoparticles, (SUN) sunitini, (OVCAR-3 and SK-OV-3) Human ovarian cancer cell line, (CuFe) copper–iron, (CoFe) cobalt–iron, (PBA) Prussian blue analogs, (PEGMA) polyethyleneglycol methacrylate, (mSiO2) mesoporous silica, (AZD5363) is a selective Akt inhibitor with therapeutic potential for tumors, (CCRF-CEM) Human acute T lymphoblastic leukemia cell line, (T-ALL) T-cell acute lymphocytic leukemia, (H-MnO_2)The hollow mesoporous MnO_2 nanoparticles, (SRF) Sorafenib , (HCC) hepatocellular carcinoma, (GPC3) glypican-3 receptors, (HL60) The human leukocyte cell line, (Drn) daunorubicin,(Lut) luteolin, (Tf) transferrin receptor, (PSMA) prostate-specific membrane antigen, (ABR) Abiraterone, (TOA) DOX/ICG-loaded TOA, (ICG) indocyanine green, (cGO) carboxylated graphene oxide, (Sili) silibinin, (NHGs) nanohydrogels, (CSSD) chondroitin sulfate A-ss-deoxycholic acid, (QDs) quantum dots, (SO) sodium oxamate, (Ce6) photosensitizer, (PLA) polylactide, (PVGLIG) synthetic peptide

Cytotoxicity:

Cytotoxicity is often associated with the detrimental effects on a specific cell line. As a result, cytotoxicity is typically initially assessed through specific in vitro assays before proceeding to *in vivo* testing (Kus-Liśkiewicz et al., 2021). Visual examination of cells using bright-field microscopy serves as a fundamental means of assessing cytotoxicity. Commonly, colorimetric techniques are employed to assess plasma membrane integrity and metabolic activity in cytotoxicity assays. The LIVE/DEAD viability test is utilized to quantify the number of decreased cells. In the context of in vitro nanoparticle cytotoxicity assays, LDH, MTT, and MTS assays are extensively employed, with MTT and MTS being particularly useful for measuring the metabolic activity of viable cells (Nikzamir et al., 2021).

Chemotherapy is the most prevalent approach for cancer treatment. However, it comes with several challenges, such as low accumulation in tumor cells and limited target selectivity (Maghsoudi et al., 2019). Nanosized drug delivery systems often exhibit prolonged systemic circulation and lower accumulation in normal organs compared to tumor tissues. Nevertheless, one of their drawbacks is the potential toxicity to normal cells in addition to cancer cells (Hafeez et al., 2021). The key to cancer therapy is to improve the specific recognition of pathological. The interaction to aptamers with nanomaterials has helped to achieve this goal by increasing the effectiveness of anticancer drugs against their targets. The ability of aptamers to identify specific epitopes on the cell surface may lead to better drug accumulation in cancer cells (Khan et al 2021). Several studies have investigated the toxic effect of drug-nanoparticles-aptamer, nanosized drug delivery systems, and free drugs against cancer cell lines (target cells), and non-cancer cell lines (non-target cells) (Table 6). The results of some previous studies have shown that cell viability was lower (i.e., higher toxicity) with aptamer-conjugated nanoparticles compared to nanosized drug delivery systems, and free drugs, while the results of other research have shown opposite results. The same applies to the safety of non-cancer or non-targeted cells. Since the results are still conflicting, more studies are needed to determine the optimal drug delivery system.

Table 6. Effect on cell viability of drug-nanoparticles-aptamer, nanosized drug delivery systems, and free drugs on cancer and non-cancer cell lines

Target & nontarget	cell line	Cell viability			Concentration	Time	Type of Therapy	Ref
		Drug	Drugs & NPs	Drugs & NPs & AP				
+	MCF-7	60%	50%	25%	4.8 μg mL−1 of 5-FU	48 h	Chemical	(Mazandarani et al., 2023)
+	OVCAR-3	54%	21%	12%	20 μM of SUN	24 h	Chemical	(Torabi et al., 2023)
-	SK-OV-3	80%	75%	74%				
+	4T1	50%,	- - - -	62%	20 μg mL−1 (CuFePBA@PEGMA@ AS1411/DOX)	48 h	Chemical	(Chen et al., 2023)
-	L929	5%	- - - -	40%				
+	4T1	50%,	- - - -	62%	20 μg mL−1 (CoFePBA@PEGMA@ AS1411/DOX)	48 h	Chemical	
-	L929	5%	- - - -	60%				
+	CCRF-CEM	8.3%	- - - -	45.9%	20 μM of AZD5363	24 h	Chemical	(Yang et al., 2023)
+	HepG2	50%	45%	18%	8μg mL−1 of SRF	24 h	Chemical	(Wang et al., 2023)
+	MCF-7	60%	50%	40%	50 μM of PTX	24 h	Chemical & photothermal	(Kadkhoda et al., 2023)
-	MDA-MB-231	55%	65%	85%				
+	4T1	80%	45%	20%	20 μM of dox	24 h	Chemical & photothermal	(Li et al., 2023)
+	MCF-7	- - - -	28%	19%	100 μg/ml	- -	Chemical & photothermal	(Işıklan et al., 2023)
+	C26	90%	95%	80%	0.60 μg/mL of SN38	24 h	Chemical	(Ramezani et al., 2023)
-	CHO	80%	80%	90%				
+	LNCaP	50%	40%	30%	30μM	48 h	Chemical	(Al Hoque et al., 2023)
-	PC3	70%	60%	60%	30μM	48 h		
+	MCF-7	55%	60%	40%	3μM (PTX)	48 h	Chemical	(Ranjbar-Navazi et al., 2023)
+	HL60	48%	42%	30%	5 μM	48 h	Chemical	(Zhu et al., 2023)

Nanoparticle Triggering:

Nanocarriers can be engineered to respond to both intrinsic and extrinsic triggers for drug release (Han et al., 2022). Internal triggers encompass variations in pH, temperature, enzyme activity, ATP levels, and hormonal responses, whether they occur intracellularly or extracellularly. External triggers, on the other hand, encompass factors such as light, ultrasound, magnetic fields, mechanical stress, and more (Virmani T et al., 2023). In practice, various nanoparticles that can change in size in response to different stimuli, including pH, UV light, temperature, and enzymatic activity, have been developed to achieve more uniform drug distribution within tumors and enhance their anti-tumor efficacy (Hu et al., 2018).

PH-Responsive Drug Delivery Systems:

PH-responsive nanoparticles have garnered significant research interest due to their ability to respond to changes in pH upon cellular internalization. Specifically, when nanoparticles are endocytosed into a cell, the pH decreases from approximately 7.4 in the bloodstream to about pH 6.5 in the early endosomal compartment and even lower - below pH 5- in the lysosomal compartment (Deirram et al., 2019). Furthermore -in nearly all solid tumors- there is a notable decrease in extracellular pH compared to normal tissues. This change is primarily attributed to anaerobic or aerobic glycolysis combined with a reduced removal of acidic metabolites (Thews et al., 2019). Tumor cells typically exhibit an extracellular pH of around 6.0, whereas normal cells maintain an extracellular pH of approximately 7.4. Additionally, while the intracellular pH of tumor cells is slightly higher than that of normal cells, the pH of lysosomes in tumor cells is lower (Shi et al., 2020).

PH-sensitive nanoparticles can exploit these varying environments for intracellular drug delivery. Upon cellular internalization through endocytosis, these nanoparticles can gradually swell or disassemble in response to the protonation of imidazole groups under acidic conditions, thereby triggering the release of loaded drugs (Guo et al., 2014). A previous study showed that altering the pH from 7.4 to 5.0 led to a 2.8-fold change in particle diameter (Hu et al., 2007).

Therefore, the efficiency of pH-dependent drug release has been a subject of investigation in many of the drug delivery studies. Most studies indicated that the most effective drug release occurred under acidic pH conditions. This aligns with the expected behavior upon nanoparticle entry into cells and the altered environment within tumors, as mentioned earlier. Table 7. presents recent studies on pH-responsive nanomaterials for anticancer drug delivery.

Photodynamic Therapy (PDT) and Photothermal Therapy (PTT)

PDT and PTT are effective cancer treatments, but complete eradication of cancer cells is not guaranteed, potentially leading to recurrence. Combinations of these therapies are explored to address limitations (Elbialy et al., 2019). In chemo-photothermal cancer therapy, researchers investigate the co-delivery of multiple agents using NPs for drug delivery and photothermal effects (Siddique et al., 2020). Controlled release mechanisms prevent premature drug release, targeting tumor cell necrosis and overcoming drug resistance (Zhang et al., 2020).

PDT is an emerging noninvasive treatment modality that relies on the use of a photosensitizer and light to generate reactive oxygen species (ROS) that are capable of killing cancer cells, offering a noninvasive cancer treatment with precise control (Zhen et al., 2019).

PTT represents a form of cancer therapy in which NPs are embedded within the tumor and generate heat in response to exogenously applied laser light. Using NPs as photothermal agents can lead to the release of heat, which can directly damage tumor cells (Siddique et al., 2020).

Table 7. Recent studies on pH-responsive drug delivery system

drug-nanoparticle-aptamer	Sensitive	Release	Time	Ref
5-FU-GA-Cs-CQD-Apt	pH 5.4	80%	48 h	(Mazandarani et al., 2023)
	pH 7.4	56%		
MSNP-PEG/SUN-MUC16	pH 5.4	58.6%	48 h	(Torabi et al., 2023)
	pH 7.4	14.1%		
CuFePBA@PEGMA@AS1411/DOX	pH 5.0	56%	48 h	(Chen et al., 2023)
	pH 7.4	23%		
CoFePBA@PEGMA@AS1411/DOX	pH 5.0	75%		
	pH 7.4	24%		
mSiO2-Au-AZD5363	pH 5.5	57.5%	48 h	(Yang et al., 2023)
	pH 7.4	14.8%		
H-MnO2-SRF-APT	pH 5.5	90%	24 h	(Wang et al., 2023)
	pH 7.4	18%		
ΔPSap4#5-ABR-NP	pH 5.0	92.4%	672 h	(Al Hoque et al., 2023)
	pH 7.4	73%		
Ap-NHG-QDs-PTX-SO	pH 5.8	70%	168 h	(Ranjbar-Navazi et al., 2023)
	pH 7.4	45%		

This damage may be attributed to the fact that DNA repair processes, and cell membrane integrity, are severely affected by heat shock, enhancing permeability, and leading to the accumulation of a higher concentration of the drug at the tumor site (Faid et al., 2023). PTT-induced necrosis is the most traditional cell death pathway, which can lead to the release of large numbers of tumor fragments and many DAMPs "danger signals," such as heat shock proteins. These signals can be considered antigenic and immunostimulatory signals to activate the immune system (Han et al., 2022). Photosensitive nanoparticles offer a multitude of different applications, including controlled drug release resulting from physical/conformational changes in the delivery system in response to light of a specific wavelength (Pan et al., 2021).

Table 8 presents the results of previous studies in which high spatial and temporal on-demand drug release was achieved via phototriggerable. The results showed improved drug release when it was triggered by NIR laser irradiation/pH compared to pH-dependent release.

Table 8. Recent studies on drug release triggered by NIR laser irradiation/pH

drug-nanoparticle-aptamer	Irradiation/pH	Release	Time	Ref
PTX/PEG-AuNPs-MUC1	pH 5.4	65%	60 h	(Kadkhoda et al., 2023)
	Under 810 nm NIR irradiation + pH 5.4	75%		
TOADI	pH 5.0	30%	24 h	(Li et al., 2023)
	NIR irradiation (808 nm, 1.0 W/cm2, 5 min) + pH 5.0	62%		
Fe3O4-GO-Ce6-Apt-Pac	pH 5.5	35%	72 h	(Işıklan et al., 2023)
	Under 808 nm NIR irradiation + pH 5.5	52%		

Temperature-Sensitive Drug Delivery Systems

Hyperthermia is an adjuvant therapy performed in combination with chemotherapy and radiotherapy to enhance cytotoxic effects. Increased cytotoxicity, and increased drug absorption through tumor vascular permeability, are the advantages of adding hyperthermia to chemotherapy (Mirrahimi et al., 2020). In addition, drug release may also depend on environmental temperature changes. Compared to healthy tissues (37°C), the tumor environment has a higher temperature (~ 40–42°C), which depends on its metabolic activity and vascularization (Amin et al., 2020).

Table 9 presents the results of previous studies in which drug release was triggered by temperature/pH. The results showed improved drug release at temperature 42, which was close to the tumor environment.

Table 9. Recent studies on drug release triggered by temperature/pH

drug-nanoparticle-aptamer	pH/ temperature	Release	Time	Ref
Fe3O4-GO-Ce6-Apt-Pac	pH 5.5 & 45 °C	47%	72 h	(Işıklan et al., 2023)
	pH 5.5 & 37 °C	36%		
Apt-cGO-DOX-Sili	pH 5.5 & 42 °C	70%	72 h	(Shahidi et al., 2023)
	pH 5.5 & 37 °C	50%		

Oxidative- and Enzyme-Responsive Drug Release Systems

Nanocarriers are precisely designed to be sensitive to various internal stimuli within the body, with particular emphasis on the redox response of enzymes.

This innovative approach ensures precise drug delivery, minimizes the risk of drug leakage into the bloodstream, and guarantees drug release specifically at the tumor site. Remarkably, this delivery system can even surpass expectations without the need for additional external stimuli (Li et al., 2020). One such critical factor in this context is glutathione (GSH), a thiol-containing tripeptide. GSH is found in significantly higher concentrations within the cell cytoplasm compared to its levels in the blood plasma. Notably, tumor cells exhibit much higher cytosolic GSH concentrations compared to normal cells (Sauraj et al., 2021).

Cancer cells exhibit distinctive enzymatic activity driven by their specific requirements for proliferation, growth, and metastatic invasion. Leveraging the heightened intracellular and extracellular enzyme expression in these cells, an enzyme-responsive drug-release system can be engineered (Yadav et al., 2021). Among these enzymes, matrix metalloproteinases (MMPs) stand out as overexpressed proteases in tumorous tissues across all stages of cancer (Vaghasiya et al., 2021).

Table 10 presents the results of previous studies in which drug release was investigated in the presence and absence of GSH and MMP-2 at pH 7.4. The results showed that MMP-2 significantly enhanced the release process. This is due to its role in dispersing the polymers carrying the drug and thus releasing it. GSH also enhanced drug release, but its role was to mimic body fluids in the presence of cancer cells.

Table 10. Recent studies on oxidative- and enzyme-responsive drug-release systems

drug-nanoparticle-aptamer	Oxidative/ enzyme	Release	Time	Ref
D-ACS	(PBS +10 mM GSH)	88.3%	96 h	(Yu et al., 2023)
	PBS	50%		
SN38-pep-NPs	(PBS +10 mM MMP-2)	80%	100 h	(Ramezani et al., 2023)
	PBS	11%		

(ACS) AS1411 aptamer-modified chondroitin sulfate A-ss-deoxycholic acid, (D-ACS) The ACS conjugation with Dox

Aptamer-Controlled Release of Nanoparticle Cargo:

Controlled drug release can also be achieved using an aptamer-gated mechanism. This mechanism relies on aptamer-target binding interactions as molecular stimuli to stimulate the release of the drug from nano-sized reservoirs. These systems use aptamers as guidance elements to direct drug nanocarriers to the targeted disease cells, but also use this biorecognition event as an open/close checkpoint to control drug release at specific sites (Thevendran et al., 2020). Two mechanisms of "aptamer-gated systems" have been described, the snap-top aptamer-based-gating systems (Zhu et al., 2011), and the nanovalve aptamer-based-gating systems (Abelow et al., 2010).

In the snap-top system, mesoporous silica nanoparticles (MSNs) were capped with gold (Au) nanoparticles modified with ATP aptamer. Through competitive displacement, gold particles were uncapped -in the presence of trigger molecule ATP- and the guest molecule was released (Zhu et al., 2011).

Likewise, nano valve systems also rely on aptamer-gated MSNs pores, but instead, utilize adsorption of the immobilized aptamer strand near the pore surface to block the openings, while converting to an open-state only in the presence of an aptamer-specific target molecule (Abelow et al., 2010; Thevendran et al., 2020). In addition, nano valves were developed to open and close pores in response to pH, light, temperature, and redox (Kavruk et al., 2015). However, both systems are limited by other factors such as being only applicable to materials that can form mesoporous structures, show sudden drug release, but decrease rapidly over time, or the desorption of the aptamer due to changes in surrounding pH or ionic strength that can indirectly cause aptamer-based gates to not close properly (Thevendran et al., 2020). MSN nanomaterials are suitable for controlled drug delivery, due to their unique physio-chemical properties such as large specific surface area and pore size, controllable particle size, high drug loading capacity, and remarkable biocompatibility and stability (Song et al., 2017). Most reports on aptamer-based gating silica nanoparticles (Pascual et al., 2017; Zhang et al., 2015) use aptamers that their target ligands present on the cell's surface, which causes the release of the drug close to the surface, but not into the cell. This reduces the efficacy and specificity of the therapy. To solve this problem, an effective strategy was developed in previous research in which bivalent aptamers consisting of ATP and AS1411 sequences were used to provide separate targeting and gating properties. Using this strategy, AS1411 targets the formulation toward nucleolin overexpressing cancer cells, and after penetration into the cells and facing high levels of ATP in the cancer cells cytoplasm, the drug releases by the interaction of ATP molecules with the second part of bivalent aptamer, the ATP aptamer (Charbgoo et al., 2021). Separated gating and targeting approach was also performed using hyaluronic acid-targeted nanocarrier based on silica nanoparticles gated with peptide nucleic acid and ATP aptamer and loaded with doxorubicin (Kazemi et al., 2022). However, the encouraging results of aptamer-based gating are expected to open great possibilities for future therapeutic applications in the field of drug delivery (Ozalp et al., 2011).

CONCLUSION

The current review focused on recent achievements in the field of targeted anti-cancer drug delivery based on aptamers, nanoparticles, and aptamer-conjugated nanoparticles. The reviewed literature revealed that nanomaterials play a crucial role in targeted therapy, although they often lack specificity. Aptamers, on the other hand, offer a high degree of specificity towards cancer indicators. These two approaches have been utilized individually in the treatment of cancer, each having its strengths and limitations. However, when combined, the limitations of both approaches are mitigated, control is enhanced, and the results have shown great promise. We hope that this review will provide additional information that will facilitate advanced applications of nanoparticle/ aptamer-based drug delivery systems for cancer therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION RATE STATEMENT

Conceptualization, M.M.A. and D.J.; methodology, M.M.A. and D.J.; validation, M.M.A. and D.J.; formal analysis, M.M.A.; investigation, M.M.A. and D.J.; resources, M.M.A.; Data Curation, M.M.A. and D.J.; writing- original draft preparation, M.M.A.; writing-review & editing, D.J.; visualization, M.M.A.; Supervision, project administration, M.M.A. and D.J.; All authors have read and agreed to the published version of the manuscript.

DECLARATION

It is noteworthy that the visualization of the nanoparticle in Figure 5 presented in this article was generated using Bing.

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