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REVIEW ARTICLE

Prospects of Targeted Gene/Drug Delivery Vectors and their Potential Use in Cancer Therapy

Venkanna Muripiti[1,#], Venkatesh Ravula[2] and Srilakshmi V. Patri[3,*]

[1]*Department of Education, Central University of Kerala, Kasarasod-671316, Kerala, India*
[2]*Institute for Stem Cell Science and Regenerative Medicine, Bengaluru-560065, Karnataka, India*
[3]*Department of Chemistry, National Institute of Technology, Warangal-506004, Telangana India*

Abstract:

Targeted gene and drug delivery vector developments have completely changed the therapeutic intervention by providing previously unheard-of levels of accuracy and efficacy in treating various illnesses. Cancer is one such fatal disease plaguing people across the globe. This review article highlights the potential uses of targeted delivery systems in the field of cancer treatment while providing a thorough examination of the state of the art. Chemotherapy and radiation therapy are being used to cure cancer, yet they can be frequently ineffective and have serious adverse effects. Novel techniques for therapy have to be designed. Existing chemotherapy is being superseded by particular gene therapy used for genetic diseases. Therefore, to deliver the therapeutic agent to the targeted place, a carrier or vector is needed. The current review is focused on targeted gene/drug delivery vectors concerning i) cationic lipids that target single receptors ii) ligand-peptide conjugated cationic lipids iii) modalities for targeting dual ligands for cancer therapy iv) passive *versus* active targeting v) properties of nano-formulations for gene and drug delivery. The most recent developments in lipid customization for certain receptors overexpressed in cancer cells are covered to reduce side effects and improve treatment results. By delving into the above areas, this review presents a broad overview of the changing field of cationic lipids in cancer therapy, giving scientists and medical professionals insightful knowledge about the many strategies for ensuring precise and efficient drug delivery in the battle against cancer.

Keywords: Gene therapy, Targeted receptors, Off-target, Cancer therapy, Dual-targeting, Drug delivery vector.

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1. INTRODUCTION

Cancer is an ailment produced by the unrestrained disunion of cells and their spread into surrounding tissues. Among the most complicated sicknesses and the primary cause of mortalities worldwide is cancer [1]. Changes to DNA can lead to cancer. Most of the genetic aberrations that cause cancer take place in regions within the genome known as genes [2]. To treat cancer, chemotherapy is being used. During chemotherapy treatment, the patient may experience exhaustion, nausea, and gastrointestinal difficulties, including bloating or diarrhea, loss of hair, blisters in the mouth, and problems with the skin [3]. Hence, chemotherapy is superseded by gene therapy. Owing to this, gene therapy involves inserting a normal gene into an individual's genome to repair a mutated gene responsible for a disease [4]. A normal gene transfers a different chromosomal site from a defective allele into the nucleus of a mutant cell [5]. The process may potentially restore a mutation, then a new mutation may arise if a normalgene is integrated into an alternate functional gene [5]. Gene therapy aims to tackle genetic issues at their root cause. The gene itself cannot reach the targeted place. Henceforth, to deliver genes into target places, vectors are needed, and these vectors are two types such as non-viral vectors and viral vectors [6]. The non-viral vectors that can be generically categorized as automobiles made of polymers: a range of polymers, such as cationic polymers, polyethyleneimine, chitosan, polyethylene glycol, mannose, and poly (d, l-lactic-co-glycolic acid) (PLGA), can transfer genes both *in vitro* and *in vivo* [7, 8]. Notably, biomaterials made from cationic lipids, which offer various benefits including simplicity of manufacturing, cell targeting, which is and a low immune response associated with their use, are being intensively studied for pDNA/mRNA delivery mid-non-viral carriers [9 - 13]. Consequently, the therapeutic gene has to be delivered to the patient's target cell using the vector, which is integrated into DNA in the nucleus, correcting the damaged or mutant gene [6, 14]. Fig. (**1**) depicts the process of gene delivery using cationic lipid-derived liposomes. Among the biomaterials made

* Address correspondence to this author at the Department of Chemistry, National Institute of Technology Warangal, Telangana- 06004, India;
E-mails: patrisrilakshmi@nitw.ac.in, patrisrilakshmi@gmail.com
#This author contributed equally to this work

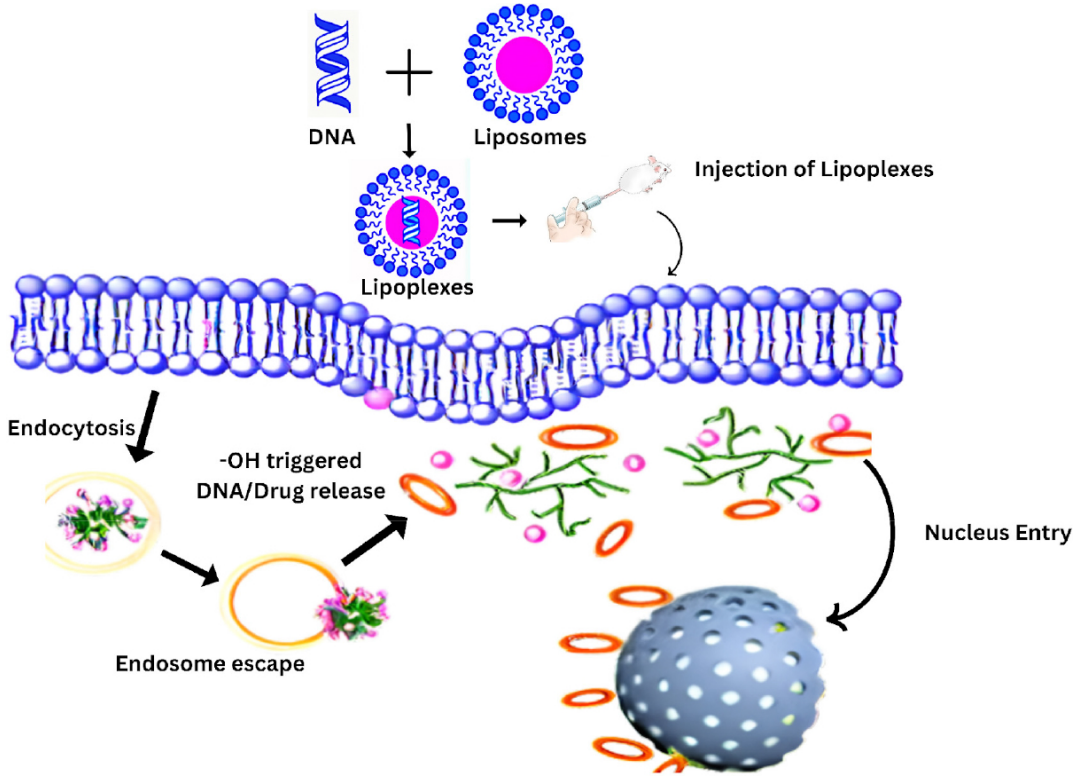

Fig. (1). Schematic mechanism of gene/drug delivery system.

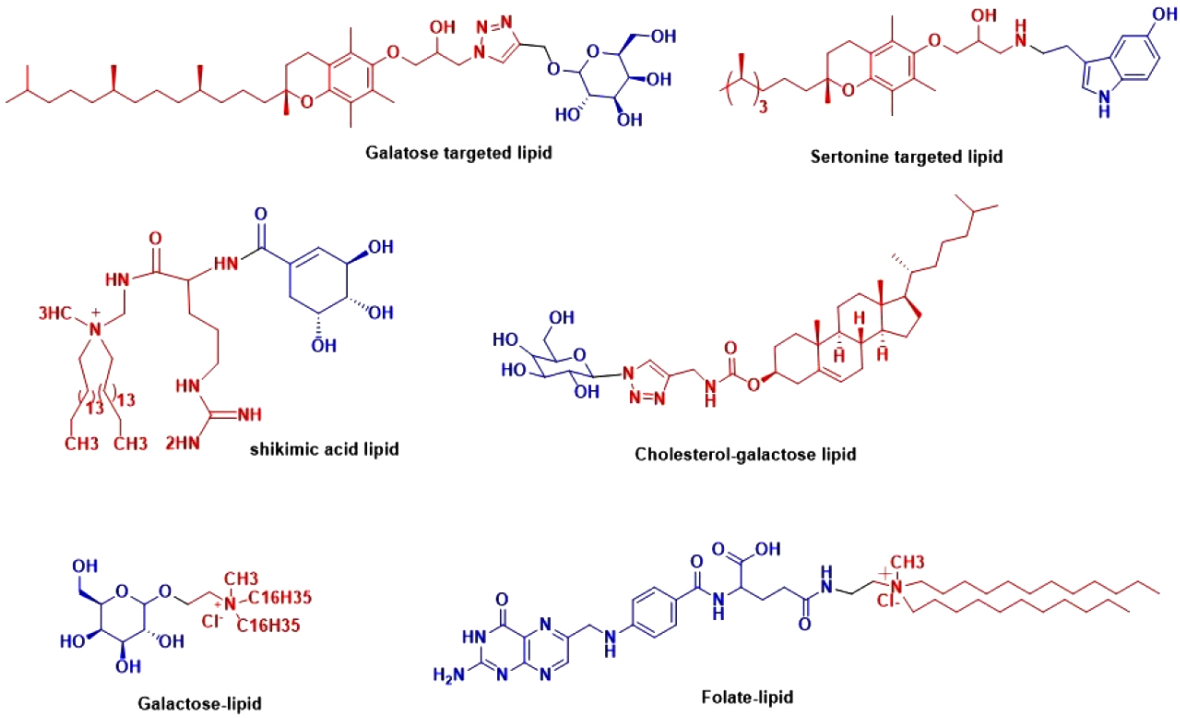

Fig. (2). Examples of targeted cationic lipids.

from cationic lipids, targeted cationic lipids are gaining increasing priority due to their high specificity to targeted places, minimal toxicity, no pathogenicity, and simple pharmacologic manufacture [15 - 19]. The current review addresses four distinct focal points in relevance to cationic lipids, each shedding light on the innovative strategies employed to enhance targeting specificity and efficacy, i) cationic lipids that target single receptors ii) ligand-peptide conjugated cationic lipids iii) dual ligand-targeting lipids, iv) passive *versus* active targeting and v) Benefits of nano-formulations for gene and drug delivery.

1.1. Cationic Lipids that are Targeting Receptors

Primary non-viral gene delivery approaches employed non-specific mechanisms of pDNA complex hail onto cells, which seemed necessary for non-specific endocytic uptake by maximum cells [20, 21]. After that, pDNA gets into the cell, and contact with the plasma membrane could have been facilitated by lipids that can encapsulate pDNA [22]. Although these gene transfer techniques are effective in a wide variety of cell types *in vitro*, their potential for therapy *in vivo* requires more characteristics of enhanced delivery [23]. Nevertheless, the plasmid comprised cell-specific promoters of genes ubiquitous delivery of a gene to an intended tissue requires elevated and possibly hazardous, vector doses due to non-specific uptake *in vivo* [24]. This issue is resolved by conjugated gene transfer vector ligands, which allow for lower and safer vector doses while enabling tissue targeting [25]. Fig. (**2**) shows some examples of cationic lipids with various targeting ligands.

Various ligands with sugar-like moieties were also synthesized to targeted glycoproteins in extracellular and intracellular environments (Fig. **3**). Asialoorosomucoid, which was chemically linked to polylysine in one of the first targeted vectors, both *in vitro* and *in vivo,* guided gene transfer to asialoglycoprotein receptors on hepatocytes [26]. The vector's target-specificity was shown by the asialoglycoprotein competitive conquest of hepatocyte gene expression [27]. In every instance, the vector-aided RNA receptor-mediated endocytosis helps pDNA enter the targeted cells [8, 28]. However, the inability of each vector to escape the cellular endosome encasing it after endocytosis ultimately led to less-than-ideal levels of delivery [29]. Since then, many ligands have been examined for receptor-targeted transfer of genes [30]. Whether or not endocytosis takes place at the target receptor greatly influences ligand selection [31, 32]. More ligands have been investigated and tested, including neuregulin, Transforming Growth Factor (TGFα), insulin, folate, Fibroblast Growth Factor (FGF), and integrin binding motifs [33]. To control gene transfer, antibodies made against certain cell-specific receptors have also been utilized, which target antibody-directed molecular conjugates, including human epidermal growth factor receptor 2 (ErbB2), Cluster Differentiation 3 (CD3), Cluster Differentiation 5 (CD5), and Epidermal Growth Factor (EGFR) [34, 35]. The capacity of the antigen to induce receptor internalization is crucial to the effectiveness of an antigen-directed molecular conjugate [36, 37]. Further instances of receptors that target include integrins and the tissue factor (Tf) receptor, the ErbB receptor, and the folic acid receptor [38, 39]. The type of cell entrance mechanism that is going to be activated following fusion is a further factor for targeting, along with the receptor-targeted, which influences the final selection of payload [31, 40, 41].

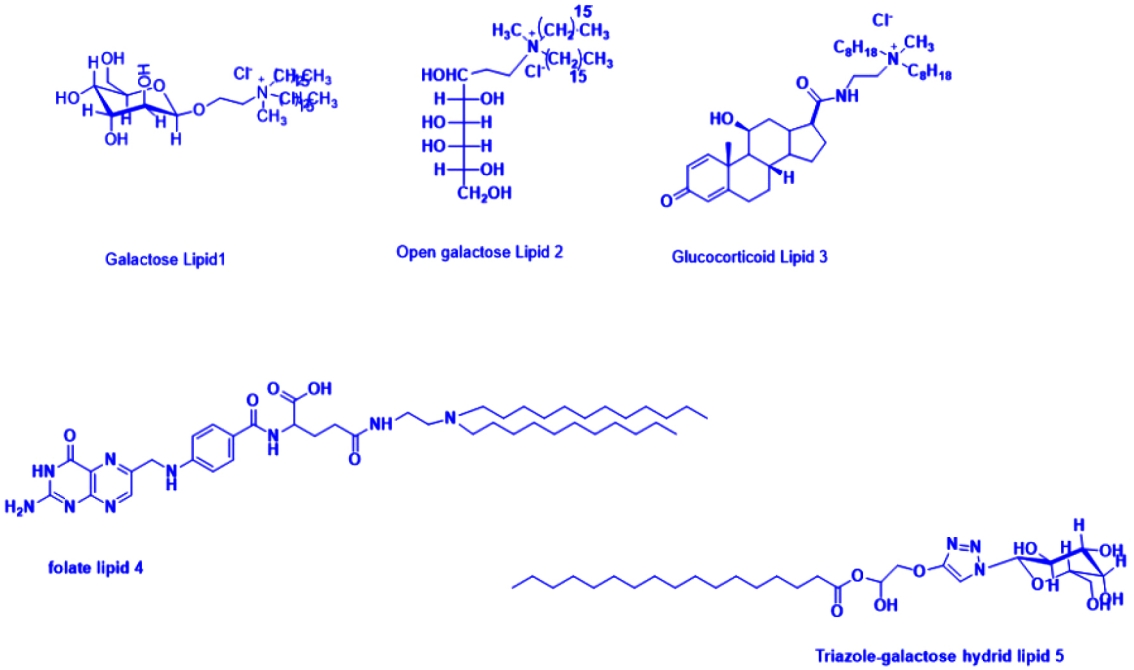

Fig. (3). Examples of cationic lipids with carbohydrate ligands designed for targeted delivery.

Table 1. Targeting ligands.

S.No.	Receptor Name	Recognizing Ligands	Name	References
1	Toc-Galactose	Asialoglycoprotein receptor	Small molecules	[17, 45]
2	Folate receptor	Folate receptor	Small molecules	[46 - 49]
3	Serotonin	Serotonin	Small molecules	[50, 51]
4	αvβ3 integrin receptor	arginine-glycine-aspartic acid (RGD)	Peptides	[52, 53]
5	vascular endothelial growth factor (VEGF)	Hepatopeptide ATWLPPR	Peptides	[54, 55]
6	Pegaptanib	VEGF receptor	Aptamers	[56, 57]
7	Transferrin receptor	Transferrin	Proteins	[58 - 60]
8	Luteinizing hormone-releasing hormone (LHRH) receptor	LHRH	Proteins	[61, 62]
9	Herceptin	Her2/neu	Antibodies	[63, 64]
10	CD 19 antigen	CD19 antigen (human, B-cell lymphoma	Antibodies	[65, 66]
11	Mannose receptors	Mannosylated polyether glycol phosphatidylethanolamines ligand	mannose-mimicking di-shikimate- and guanidine	[67 - 69]
12	estrogen receptor	estrogen	DPPE-PEG-ES	[70]

The targeted receptor and cell type may affect the vector's choice of endocytic route [42, 43]. As a result, it is common to practice using tissue-specific or overexpressed ligands on tumor cells to minimize adverse effects on other healthy tissues [44]. Targeted nanocarriers have been created using various targeting ligands (Table **1**) [45 - 70].

1.2. Ligand-peptide Comprised Cationic Lipids

Peptides are connected to well-ordered amino acids, which can be used as therapeutic agents due to their advantages, such as least toxicity, immunological modulation, and cell signaling [71, 72]. Peptides are widely utilized for enhancing cationic polyplexes because of these benefits [73]. Research investigations have shown that peptides trigger 40-15% of all interactions between proteins in human cells. In consequence, peptide-containing vectors are being used as non-viral vectors for gene/drug delivery [74]. For this reason, these peptides can tightly pack the pDNA, produce against degradation enzymes, ability to bind to particular receptors of the cell membrane, disrupt the membrane of the endosomal cavity, and ability to transfer gene payload to the nuclei [75, 76]. Basic residues, including lysine or arginine, are abundant in cationic peptides used as a target-specific delivery of vectors [76]. This vector itself can send signals for nuclear localization that facilitates the introduction of DNA into the cell's nucleus thanks to a short amino acid pattern obtained from viral proteins [77]. In non-viral gene delivery systems, peptides can be employed as functional motifs to design the optimum gene carrier and get beyond current limitations in gene delivery [78, 79]. To enable effective gene transfection, non-viral carriers are decorated using diverse function-enhancing peptides [80]. The ability of the HIV-derived Polypeptide Transduction Domain (PTD) to enter cells was established by Frankel and Pabo *et al*. in 1988 [81, 82]. The greater than eight arginine amino acids in the synthesized cationic peptides polyarginine allowed it to carry a payload [83, 84]. Several cellular matrix proteins contain the arginine-glycine-aspartic acid (RGD) sequence peptide, which targets αvβ3integrin receptors [85]. While the peptide itself has been extensively utilized in bioengineering, the finding of RGD and the understanding of how RGD attaches to integrins has led to the fabrication of a variety of medications and investigations [86] siRNA/amphiphilic dendrimer delivery nanoparticles were developed by Dong *et al*. equipped with a dual targeting peptide, RGDK was able to protect siRNA from degradation and enhance siRNA delivery [87, 88]. Others have developed a variety of RGD-containing peptide analogs with improved biological and pharmacokinetic properties by introducing variable flanking amino acids, cyclization, or substitution of the component of the amino acids, while a few investigators have adapted gene delivery vectors with the linear RGD sequence to increase their transfection efficacy [89].

1.3. Modalities for Targeting Dual Ligands for Cancer Therapy

Nanoplatforms for delivering drugs that target two different ligands are thought to be a potential method for improving chemotherapy's selectivity [44, 90]. Although each ligand may separately identify receptors on the cell membrane surface and direct drug nanocarriers to various cells, severe off-target delivery has been found in current dual-ligand targeting nanoplatforms [91, 92]. A dual-ligand combinatorial targeted nano platform has been developed to get around this obstacle and direct chemotherapy therapy precisely to cancer cells that are concurrently expressed by both receptors [93 - 95]. Growth signals that are transmitted by receptors and are frequently elevated in tumor cells are crucial for the formation and progression of tumors [96]. Members of the EGF receptor family, such as EGFR [97], HER2 [98], HER3 [99], and HER4, and the IGF-1 receptor (IGF-1R), are two examples. These receptors control cell proliferation [100], survival, differentiation, and migration [101]. Active targeting relies on ligands' recognition and affinity towards tumor cell surface receptors, which are easily influenced by the dynamically changing nature of cancer cell receptors [102 - 104]. By eliminating the uncontrolled and irregular distribution of single-ligand nanomedicines, dual-ligand strategies can enhance the process of navigation, specific targeting, absorption by cells, and the effectiveness of therapy of cancer

nanomedicines [105, 106]. The potential of nanoparticles with specific ligands to improve cancer cell identification, which in turn increases both the precision and the curative value of their payloads, has attracted a lot of attention [107, 108]. Qi Chang Zheng *et al*. developed a dual-targeting nanoparticle for introducing small interfering RNA for hepatocellular carcinoma. Their experimental results showed that GCGA-siPAK1 in particular, improved the NP targeting capability and encouraged siPAK1 cell uptake. The result was that the cells treated exhibited large reductions in cell growth, invasion, and relocation, along with a significant increase in cell death [109]. Meanwhile, Shi Zhang Qiao's research group reported that mesoporous silica nanoparticles made with folic acid and dexamethasone are dual-targeting ligands specifically targeted at cancer cells [110]. According to Jose *et al*., docetaxel-loaded Tf-conjugated PLGA nanoparticles demonstrated promise anticancer effectiveness by halting tumor activity during the G2/M phase of mitosis [111]. The research group, led by Chi-Hwa Wang, developed PTX-MNP-PLGA nanoparticles, which were Tf-conjugated magnetic PLGA NPs had shown antiproliferation and higher cellular absorption in U-87 cells [112]. Rebekka Spellerbero *et al*. developed dual-targeted NIS DNA plasmid complexes with targeting ligands for the Transferrin Receptor (TfR) and the Epidermal Growth Factor Receptor (EGFR) to allow active migration across the Blood-Brain Barrier (BBB) followed by target of tumor cells. *In vitro*, transfection studies were used to evaluate the TfR- and EGFR-dependent transfection efficiency and sodium iodide symporter (NIS)-specific iodide absorption of dual-targeted polyplexes [113]. The goal of this research was to develop a double receptor targeting, Blood-Brain Barrier (BBB) piercing peptide-modified Polyethyleneimine (PEI) nanocomplex that could effectively deliver the glioma-treating, angiogenesis-inhibiting secretory endostatin gene (pVAXI-En) [114].

Ke Zhang's research group reported that with dual-adjuvanted spherical nucleic acids, TLR9 activation in cancer immunotherapy is increased. They found that a self-adjuvant strategy based on spherical nucleic acids (SNA), phosphodiester oligonucleotides, and vitamin E can function as an efficient anticancer vaccine needing a carrier [115]. In general, adenoviral vectors are being used as vectors for Prostate Cancer (PCa) targeted therapy. Hence, prostate cancer-specific transferrin medication targeted therapy was improved by an adenoviral vector. To induce and stimulate transferrin-receptor expression on the PCa, a functional PCa-specific gene probe is specifically delivered through an adenoviral vector. As a result, there is a noticeably increased accumulation of nanoscale transferrin-doxorubicin (Tf-DOX) [116] protein-drug conjugates, which is accompanied by a noticeably greater inhibition of PCa tumor growth. A significant issue is the effective transport of medicines *via* the Blood-Brain Barrier (BBB) to the brain. By using bio-orthogonal chemistry, a simple technique of Dual Site-Selective Functionalized (DSSF) poly (-amino esters was created to encourage brain nerve regeneration [117]. Min Li and colleagues examined how they interact between these two targeted units in hepatocellular carcinoma (HCC). GCGA-siPAK1, in particular, improved the NP-targeted capability and encouraged siPAK1 cell uptake. The result was that treated cells showed dramatic reductions in cell division, invasion, and migration as well as a noticeable increase in cell death [109]. *In vitro* and *in vivo* tests revealed that the polyethylene glycol-distearoylphosphatidylethanolamine-containing ligands for Transferrin (Tf) and Hyaluronic Acid (HA) had much greater transfection effectiveness over undecorated DNA-NLCs and single ligand-decorated NLCs [118]. Therefore, delivering a medicine or gene has become critically dependent on ligand-targeting dual receptors. Table **2** summarizes various studies developing dual-targeted nanovectors [119 - 125].

1.4. Passive *versus* Active Targeting

Efficient delivery of the cancer drug into the targeted place successfully results in substantial tumor accumulation while sparing the surrounding healthy tissues. The Enhanced Permeability and Retention (EPR) effect [126], which refers to the passive localization of numerous medicines and drug carriers as a result of its invasion across leaky vasculature, is extremely effective in treating tumors [91]. A network of blood arteries must develop swiftly to fulfill the tumor cells' demand for oxygen and nutrients as the tumor mass develops dramatically, which leads to vessel walls with a large pore, allowing large nanoparticles to extravasate into tumor masses [127]. A rapidly developing tumor that succumbs to a lack of functioning lymphatic system limits the nanoparticles and improves the accumulation, which can passively target tumors by freely passing *via* large pores and achieve maximum intratumoral accumulation. Contemporary nanomedicines for solid tumor treatment rely on the EPR effect to ensure substantial drug accumulation, increasing therapeutic efficacy [128]. Because it doesn't target cell types that express the required targeting ligand, this drug delivery method is referred to as passive targeting. There are issues when using the EPR effect for passive tumor-targeting medication delivery [129].

Table 2. Overview of various studies focused on dual or multi-receptor targeted liposomes.

S. No	Targeting Molecule	Name of Cancer Cell Line	Name of Liposomes	Name	References
1	Asp_8 and folate	MDAMB-231 cells (Breast cancer cells)	A/F-LS	Small molecules	[119]
2	Tf and Pen	U87 cells (glioblastoma cells)	Tf-Pen liposomes	Small molecules	[120]
3	Tf, TAT, and QLPVM	U87 cells and glial cells	Tf-CPP liposomes	Peptide	[121]
4	Fru, RGD, and PXT	4T1 Cells (Breast cancer cells)	Fru+RGD-Liposomes	Peptide	[122]
5	Tf and R8	A2780 cells (ovarian carcinoma)	R8 and transferrin (Tf) (Dual DOX-L)	Small molecules	[123]
6	Glu6 and RGD	MDAMB-231 cells (Breast cancer cells)	PTX-Glu6-RGD-Lip	Peptide	[124]
7	Glu_6 and FA	MDAMB-231 cells (Breast cancer cells)	Glu6-FA-Lip	Small molecules	[125]

Due to severe hypoxia, the EPR effect, a distinguishing characteristic of solid tumors, is missing in the center of the metastatic or bigger tumor masses. Clinicians may use delayed angiotensin II infusion, topical NO-releasing drugs, photodynamic treatment, or hyperthermia-mediated arterial permeabilization in solid tumors to artificially boost the EPR effect [130].

Through active targeting, tumor cells can actively take up nanoparticles. EPR does not stimulate the uptake of nanoparticles into cells despite their necessity for various treatment modalities requiring drug activation within the cell nucleus or cytoplasm [9]. Likewise, the delivery of nucleic acids, such as DNA, siRNA, and miRNA, to the targeted place requires genetic therapies to escape these molecules from the endosome [131]. In addition, active targeting is crucial in upcoming nanoparticle therapies due to the heterogeneity of EPR and its varying strength across different tumors and individuals. The majority of nanotechnology-based methods, approved or undergoing trials, rely on the EPR effect for improved intracellular absorption, trafficking, and penetration of physiological barriers in future monotherapies.

1.5. Properties of Nano-formulations for Drug and Gene Delivery

Because of their small size (10 nm to 100 nm), nano-formulations have gained significant importance. They can enter and penetrate the various organs required by slipping through the gaps in the basement membrane. Another benefit of these compounds is that they can be used as materials that release their substance in response to certain stimuli [132]. Recently, researchers are have also focused on developing biomaterials from natural sources such as cellulose nanocrystals, to directly impact the enzyme activities that govern various disease conditions [133, 134]. When creating a nanodrug, there are a few key characteristics that must be taken into account. Formulations should protect the drug or gene of choice from the adverse effects of pH, enzyme attack, and potential biochemical breakdown. The active agent must be easier to transport from the administration site to the action site [135]. Furthermore, the composition should allow for the application of lower dosages to yield a strong pharmacological effect and release the payload in its active form at the intended site. After formulation, there is frequently dynamic interaction between the payload and the carrier. There is a constant interchange because some molecules may bind to the complex, and some may disassociate from it. This dynamic interaction does not always reach a real equilibrium state in which the concentrations of free and bound entities stay constant across time [136]. Many examples of research indicate that choosing the right preparation methods is crucial to producing nano-formulations [137] with the right characteristics for a certain drug delivery application [138]. Drugs can be delivered directly to the site of action using nanoparticles designed to target specific cells or tissues. Reducing exposure to healthy tissues may result in fewer off-target effects and a lower overall dose for the medicine. It is critical to developing nanoformulations that release the medicine gradually over time. This will extend the therapeutic effect and avoid bloodstream peak concentrations, which might worsen undesirable effects [139, 140]. The concentration of the active chemical in gene or drug nanoformulations can sometimes be reduced while still achieving the desired therapeutic effect. While this is one aspect, it is not the only one that might result in fewer side effects. Some formulations enable targeted or localized medication delivery to specific tissues or organs, lowering systemic exposure and minimizing adverse effects in other regions of the body. Controlled-release formulations release the medicine slowly and gradually over time, resulting in stable drug concentrations in the body. This can assist in preventing changes in medication levels that could lead to negative effects. Formulations that extend or improve medication absorption can minimize the frequency of dosage necessary to maintain therapeutic concentrations [141]. This not only increases patient compliance but it also reduces the danger of negative effects from frequent doses. Excipients in formulations, such as preservatives, stabilizers, and fillers, can occasionally cause negative effects. Formulation scientists can reduce the risk of adverse reactions by carefully choosing and optimizing excipient concentrations. Formulations that increase a medication's bioavailability can provide therapeutic benefits at lower dosages, minimizing overall drug exposure and the risk of adverse effects [142].

CONCLUSION

Nano vectors' contribution to cancer therapy has dramatically increased over the past ten years. In this review, we outlined methods for targeted gene therapy that rely on receptor-based nucleic acid carriers. The therapeutic efficacy and adverse negative consequences of nanocarrier-encapsulated medications are improved compared to free pharmaceuticals because they selectively aggregate in the cancer locations using EPR effects. Targeted vectors can boost drug delivery effectiveness and precision even more. Numerous targeted nanocarriers are being created, and their effectiveness *in vivo* has been shown. To accomplish effective drug targeting, a variety of techniques can be used, including active targeting, passive targeting, *etc*. The possibility of specific nanocarriers in the treatment of cancer is being extensively studied, although there are currently very few instances of clinical trials for commercially viable medicines. Future research ought to focus on the therapeutic application of innovative targeted nano vectors.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to itssubmission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

TGFα	=	Transforming Growth Factor
FGF	=	Fibroblast Growth Factor
CD3	=	Cluster Differentiation 3
CD5	=	Cluster Differentiation 5
BBB	=	Blood-Brain Barrier
Tf	=	Tissue Factor
PTD	=	Polypeptide Transduction Domain

EGFR = Epidermal Growth Factor Receptor

PEI = Polyethyleneimine

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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