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A REVIEW: NEW THERAPY OPTIONS USING DENDRIMERS FOR PROSTATE CANCER

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ABSTRACT
Prostate cancer remains a significant global health concern, necessitating continuous exploration of novel therapeutic strategies to enhance treatment efficacy and mitigate side effects. This review examines the emerging role of dendrimers in revolutionizing prostate cancer therapy. Dendrimers, precisely engineered nanostructures with well-defined branching, offer unique advantages, including customizable surface functionalities, controlled drug release, and the ability to encapsulate various therapeutic agents. Recent studies highlight dendrimers as promising carriers for chemotherapeutic drugs, gene therapy vectors, and imaging agents in the context of prostate cancer. Their ability to penetrate biological barriers, such as the blood-brain barrier, and selectively accumulate in tumor tissues holds great potential for improving drug delivery precision. Additionally, dendrimers exhibit reduced systemic toxicity, enhancing the overall safety profile of therapeutic interventions. This review provides an overview of recent preclinical and clinical studies evaluating dendrimer-based therapies for prostate cancer. From enhanced drug delivery to targeted gene silencing and imaging modalities, dendrimers present a versatile platform for multifaceted treatment approaches. Furthermore, we discuss the challenges and future directions in the development and translation of dendrimer-based therapies, emphasizing the need for rigorous clinical investigations to validate their efficacy and safety in diverse patient populations. In conclusion, dendrimers represent a cutting-edge frontier in prostate cancer therapy, offering a plethora of opportunities to improve treatment outcomes while minimizing adverse effects. As research in this field progresses, dendrimer-based therapies may soon play a pivotal role in reshaping the landscape of prostate cancer treatment.

KEYWORDS: Prostate cancer, Therapeutic strategies, Dendrimers, Nanostructures, Drug delivery, Chemotherapeutic drugs, Gene therapy vectors, Imaging agents, Biological barriers, Blood-brain barrier.

1. INTRODUCTION
Dendrimers have a highly branching tree-like design in three dimensions and a spherical shape at the nanoscale. Because of its tree-like branching structure, the term "dendrimer" is derived from the Greek word "dendron," which also means "tree".[1] In 1978, Buhleier et al. produced the first dendrimer by successfully synthesizing a cascade-like repeated structure of mono and diamine around a central core.[2] In 1995, Duan et al. described an electrically conducting dendrimer in which naphthalene diamide anion radicals were incorporated into the outermost layer of PAMAM. Together, these radicals form a -stacked network that may be used as a conductor.[3] Mon dispersity, one of the dendrimer's defining characteristics, allows for mass-production of the molecule. Since cell lysis was observed in the case of cationic dendrimers due to interaction between cell membrane (negatively charged) and dendrimer surface (positively charged), biocompatibility of the dendrimers enhanced by PEGylation, glycosylation. Nanoscale size of the dendrimers not only increases the surface area but also helps in permeation in the cells without hurdle, for example, 5G PAMAM has the same size and shape as hemoglobin (Hb) (5.5nm).[4] Dendrimers are being investigated extensively for drug delivery applications because of their potential to address problems with the present drug delivery method. Due to the current drug delivery carrier's inability to deliver drugs selectively to cancer cells while minimizing their cytotoxicity to healthy cells, an increasing number of people are losing their lives to the disease. This is where dendrimers-based nanocarriers come in.[5]

Prostate cancer overview

Cancer is primarily a cellular illness in which aberrant ce lls development, multiplication, and maturation may resu lt from modifications to a single gene or to cellular signal ling.Tumour cells become parasitic as a result of cellular mutation; they rapidly proliferate and expand their vascul ar networks to feed on blood from healthy tissues.The de velopment of a bigmultidrugresistant (MDR) tumour wit h the potential to spread to other organs and tissues is a f urther consequence of this mechanism's persistencCancer is primarily a cellular illness in which aberrant cells dev elopment, multiplication, and maturation may result from modifications to a single gene or to cellular signalling.T umour cells become parasitic as a result of cellular mutat ion; they rapidly proliferate and expand their vascular net works to feed on blood from healthy tissues.The develop ment of a big, multidrugresistant (MDR) tumour with the potential to spread to other organs and tissues is a furthe r consequence of this mechanism's persistenc.[6]

Prostate cancer is the second most common malignancy diagnosed in men and the fifth biggest cause of death worldwide after lung cancer. Prostate cancer is difficult to detect in its early stages and requires close monitoring. There was an alarming rate of new instances of prostate cancer in industrialized countries in 2018, with GLOBO-CAN 2018 estimating 1,276,106 new cases worldwide; this accounts for 7.1% of all malignancies in males.[7,8] New instances of prostate cancer are expected to increase by 26.2% by GLOBOCAN 2020, with 32.1% of fatalities occurring in Asia. In 2020, the age-standardized rates (ASR) for North America (73 per 100,000) are the highest in the world, while the ASR for Asia (11.5 per 100,000) are among the lowest of any continent. Furthermore, death rates from ASR prostate cancer in Asia continue to be lower than in Africa (16.3 per 100,000 people).[9]

1.1 Limitation of current prostate cancer treatment

Current methods of treating prostate cancer include the systemic administration of anti-cancer medications, despite their drawbacks, such as poor absorption and unwanted side effects due to their non-targeted distribution. Higher systemic dosages of cytotoxic medications are required to produce therapeutic benefits, however this increases the severity of severe side effects due to the drug's non-specific absorption by normal cells, which decreases the quantity of drug transported to the intended target cells that are cancerous.[10] Along with urine incontinence, impotence and the inability to have sexual relations are well-known negative effects of therapy for prostate cancer.[11] The majority of adverse events, such as chills, a high temperature, migraine, myalgia, profuse sweating, and flu-like symptoms, were observed during the first 24 hours after infusion and were thought to be caused by the release of cytokines. However, at this far, there has been no evidence of a higher risk of autoimmune problems. The risk of bladder and/or stomach cancers rises after radiation treatment for prostate cancer. Impotence and urinary issues are only two of the many serious problems that might arise.[12]

1.2 Role of Dendrimers as a platform for prostate cancer therapy

To meet the obstacles posed by conventional pharmaceuticals, dendrimers for applications involving drug delivery have undergone significant development in recent years.[13]

For the treatment of cancer, many dendrimer types such as poly(amidoamine), polypropylene imine, polylysine, p eptidedendrimer, and poly(ethylene glycol) are used as n anocarriers. PAMAM dendrimers were first used to treat prostate cancer because of the difficulties in delivering innovative b nanomedicines, particularly long non-coding (lnc) RNA gene therapy.[14] Due to its potential uses in DNA purification, gene transport, and controlled medication administration, magneto-dendrimers have recently garnered the interest of researchers in the biomedical area. Since magneto-dendrimers like iron oxide magnetic NPs have several functional groups, nano-scale size, and low polydispersity—all of which are necessary characteristics of effective vehicles for drug delivery for prostate cancer treatment—they may serve as carriers of nanomedicines. Additionally, magneto-dendrimers have satisfactory biocompatibility and bioavailability with a low toxicity profile.[15] Heterofunctional carbosilane metallodendrimers with [Ru(5 -C5H5) (PTA)Cl] at the focal point plus peripheral dimethylamino groups were created in order to assess potential anticancer nanotherapy against prostate cancer. PTA stands for 1,3,5-triaza-7-phosphatricyclo-decane.[16] An immunosensing signal can be amplified and electroactive molecules can be loaded onto a DNA dendrimer created by different research.[17] Prostate-specific antigen (PSA) may be detected more effectively using the FRET(Fluorescence resonance energy transfer) technique when combined with CdTe)(cadmium telluride) QDs(quantum dots) and AuNPs-PAMAM.[18]

2. **Dendrimers design and synthesis:** Dendrimers are a distinct class of repeatedly branched polymeric macromolecules with multiple limbs emanating from a central region, resulting in an almost perfect three-dimensional geometric pattern. Dendrimers can be synthesized using two primary methods: a) divergent approaches and b) convergent approaches, whose direction of synthesis differs, either outward from the center or inward toward the core, respectively. Tomalia was the first to propose distinct procedures.[19] PAMAM dendrimers contain tertiary amines and amide bonds, allowing them to engage a variety of targeting and guest molecules. Hawker and Frechet are renowned for their contributions to the development of convergent strategies for the synthesis of dendrimers.[20]

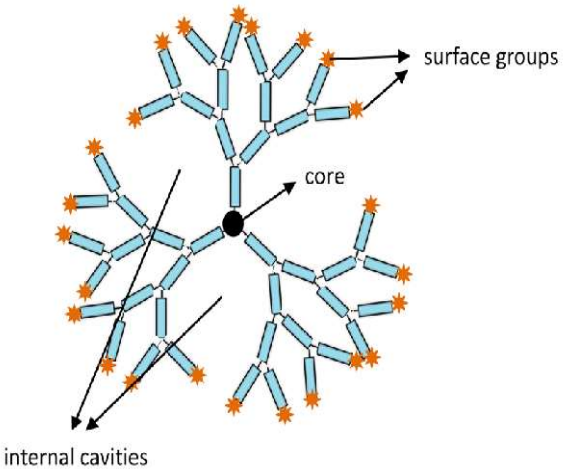


Fig. 1.1: Adopted from.[21]

In convergent methods, dendrimer surfaces are first synthesized by gradually linking surface unit monomers together. When the growing surface wedges are large enough, several are attached to a suitable core to give a complete dendrimer. Polypropylenemine (PPI) and polyaryl ethers dendrimers are synthesized by using this convergent method.[22] Dendrimers consist of a primary initiator, branches, and terminal functional groups. The initiator core is located at the center of the molecule, with branches emanating from it. The monomers affixed to the core are referred to as first generation monomers, and each first-generation monomer has two second generation monomers attached to it. In this manner, successive generations will form, with two monomers affixed to the monomer from the previous generation (Figure 1).[23] The benefit of dendrimers is their ability to be synthesized and tailored for specific applications. They are ideal drug delivery systems due to their feasible topology, functionality, and dimensions; in addition, their size is very near to that of numerous essential biological polymers and assemblies, such as DNA and proteins, that are physiologically optimal.[24]

2.1 Structural feature of dendrimers

Dendrimers are unique and highly branched macromolecules with a well-defined and symmetric structure. They possess a tree-like architecture with multiple branches emanating from a central core, leading to the formation of successive generations. Here are some key structural features of dendrimers:

Core: Dendrimers have a central core, which serves as the focal point from which successive branches emanate. The core can be a simple molecule or a complex structure and provides the foundation for the dendrimer's growth.[25]

Branches: Dendrimers exhibit a highly branched structure. These branches are formed by repeated iterations of chemical reactions, which attach monomeric units to the core or the previous generation of branches. Each subsequent generation results in an increase in the number of branches and the overall size of the dendrimer.

Generations: Dendrimers are characterized by different generations, which refer to the number of branching iterations from the core. Higher generations correspond to larger dendrimers with more branches. The number of branches in each generation follows a geometric progression, typically doubling with each successive generation.

Dendritic Periphery: The outermost layer of a dendrimer is called the dendritic periphery. It consists of functional groups that can be tailored to exhibit specific properties or to enable attachment to other molecules or surfaces. The dendritic periphery plays a crucial role in determining the dendrimer's overall chemical reactivity and interactions.

Symmetry: Dendrimers are designed to exhibit a high degree of symmetry, resulting from the controlled and sequential addition of branches. This symmetry enhances their structural regularity and allows for precise control over their properties. Common dendrimer symmetries include spherical, cylindrical, or planar structures. Size and Molecular Weight: Dendrimers can vary in size depending on the number of generations and the length of the branches. The molecular weight of dendrimers increases exponentially with each generation, making them relatively large molecules compared to linear polymers.[26]

Dendritic Cavities: Dendrimers often possess internal cavities or pockets within their structure. These void spaces can be used to encapsulate guest molecules, such as drugs, dyes, or catalysts, leading to potential applications in drug delivery, sensing, or catalysis.

2.2 Surface functionalization and targeting legends:

Targeted Nanocarrier platforms hold a great deal of promise for the delivery of cancer imaging and treatment drugs that are specific to their intended targets.[27] Despite their high targeting affinity and tumour penetration, the majority of low-molecular-weight pharmaceuticals suffer from rapid clearance, even from the tumour, potentially necessitating high and/or multiple doses for optimal therapeutic efficacy, with associated off-target toxicity. Nanocarrier systems, including inorganic nanoparticles (NPs), organic supramolecular self-assemblies, liposomes, and macromolecules, have the potential to increase the solubility and stability of encapsulated drug molecules with protracted blood circulation for enhanced therapeutic efficacy. In addition to delivering significant cargo, nanocarrier scaffolds can encapsulate multiple contrast agents and therapeutic medications. Their large surface area enables multifunctionality by conjugating a variety of targeting ligands, such as small molecules, carbohydrates, aptamers, nucleic

acid peptides, and antibodies, to enhance targeted delivery. Nanocarriers' ability to flee the reticuloendothelial system cells in the spleen and liver determines their ability to extravasate into tumours.[28] prostate-specific membrane antigen (PSMA)- There are four main categories of targeted ligands: antibodies, aptamers, peptides, and small-molecule inhibitors. Low-molecular-weight ligands have several benefits over antibodies, including simple synthesis, adaptable in situ pharmacokinetic characteristics and a reduced biological half-life, as well as biocompatibility achieved by combining with an appropriate linker or host. The isolation and analysis of the PSMA crystal structure was a landmark discovery that provided an extensive comprehension of the active location's essential connections as well as conformations.[29]

3. **DENDRIMERS IN TARGETED DRUG DELIVERY:** A drug delivery system (DDS) is a procedure for providing a pharmaceutical chemical, formulation, or technology that is used to deliver the medication in people or animals in order to provide a therapeutic effect.[30] By regulating the timing, pace, and location of medication release in the body, it increases the therapeutic substance's effectiveness and safety. It mostly includes site targeting inside the body.[31] TDD, or targeted drug delivery, is a method that primarily combines the dose form and route of medication administration. It entails putting the medicinal substance or formulation into the body, allowing it to release its active chemicals, and then moving those compounds through biological membranes to the area of action.[32] TDD is superior to traditional medication dose forms in several ways, including greater patient comforts, increased effectiveness, and drug bioavailability. TDD is the name of a credible, well-established treatments approach that creates nanoscale platforms and devices for the targeted delivery of therapeutic genes and tiny pharmacological molecules to target cells. Such delivery systems are created using a wide range of molecular techniques. When delivering treatments to the desired cells, the use of nanometer-sized entities or other types of nanocarriers is crucial.[33] Each of the three logical elements—(i) specific cellular bind through receptor ligand interaction; (ii) intracellular uptake of drug-carrying nano materials by the targeted cells via receptor mediated endocytosis; and (iii) intracellular controlled release of carried drug molecules in an active form—is essential to the concept of nano drug delivery.[34] The third phase, which involves drug release, is crucial, and it should take place in a carefully regulated way to ensure that only the targeted cell experiences the medication's biological effects.[35] The DDS, which contains metal nanoparticles, molecularly targeted nanoparticles, polymeric nanoparticles, liposomes, and dendrimers, may be employed for a variety of therapeutic purposes.[36] A appropriate root for nanocarriers that can supply the biological complex in the body is necessary for successful DDS. These drug carriers are well suited for the administration of chemotherapeutics in cancer therapy because they are passively targeted to tumours via the increased permeability and retention effect.[37]

3.1 passive and active targeting mechanism: By taking use of a special trait of tumour cells known as "the enhanced permeation and retention effect" (EPR effect), targeted distribution of anti cancer medicine made possible.[38]

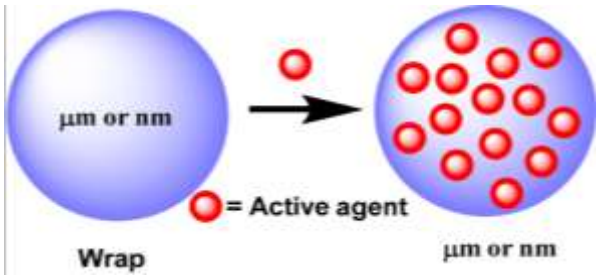
A range of ligands that bind with certain receptors overe xpressed on the surface of tumour cells may be added to the nanoparticle surface in addition to this passive targeting based primarily on size, providing selectivity for active targeting.

Another cuttingedge technique for targeted administratio n is the sitespecific release of a medication housed in a n anoparticulate system by applying external stimuli, such as hyperthermia, to a thermosensitive device.[39] Passive targeting takes use of the greater interstitial spaces between neighboring endothelial cells (200–1200 nm) seen in tumours, which improve the permeability of the endothelial blood microvasculature. As a result, the increased permeability of these blood micro capillaries makes it simpler for drug-loaded nanocarriers to extravasate into tumours, increasing accumulation and prolonging drug exposure in the tumour owing to restricted clearance. Such nanotherapeutic chemicals are passively recruited to the tumours by this increased permeability and retention (EPR) effect, even without a targeted ligand on the nanocarriers surface.[40] Active targeting, on the other hand, tries to target certain cancer cells while also using the EPR effect. The idea behind the targeted method is to target a cell surface biomarker or receptor molecule that is overexpressed in malignant cells by covalently attaching a targeting ligand to the surface of nanocarriers. a potential transporter for anticancer medications to tumours employing nanocarriers is shown in the schematic of passive tissue targeting and active cellular use.[41]

Encapsulation and controlled release of anti cancer drugs prostate cancer

Encapsulation in dendrimers has been used extensively in the biomedical field (imaging, pharmaceuticals), as well as in the food and cosmetics industries. Physical and chemical attributes of dendrimers, including their adaptability in terms of structure, capacity for self-assembly, stability, and electrostatic interaction abilities.[42] They may be employed in a variety of industries due to their ability to encapsulate molecules of the right size in internal cavities or the potential to graft molecules covalently to their perimeter.[43] Encapsulation is the process of enclosing unstable active agents in a barrier against undesirable reactions (such as oxidation

or degradation due to light, oxygen, or pH). There are two varieties of encapsulations that can be used, including (i) nano-encapsulation, which consists of extremely small capsules. (ii)Micro Encapsulation, involving larger particulates on the order of micrometers.[44]



3.1 Overcoming multidrug resistance of cancer

When an anticancer drug's effective dosage rises to an uncontrollable level, multidrug resistance (MDR) develops into a serious issue. Since many variables contribute to the development of intrinsic and acquired MDR, it is critical to have a thorough knowledge of these molecular mechanisms in order to create successful therapeutic approaches. For instance, the imbalance of angiogenic regulators, such as vascular endothelial growth factor (VEGF) and angiopoietins, results in structurally and functionally aberrant vascular networks caused by tumour angiogenesis. Because of the disorderly tumour blood flow, tumours may develop acidic and hypoxic areas.[45] Through several cellular mechanisms, such as decreased susceptibility to p53-mediated apoptosis and increased P-glycoprotein expression, hypoxia in cancer may contribute to multidrug resistance.[46] An illustration of several MDR contributions. The MDR processes connected to drug efflux mechanisms involving ATP-binding cassette (ABC) membrane transporters have received the greatest attention to date.[47] Patients who have the MDR effect may benefit more from chemotherapy medicines that are not ABC transporter substrates. This class of anticancer treatments includes anthracycline-modified medications such as annamycin and doxorubicin-peptide.[48]

4. DENDRIMER IN IMAGING

Dendrimers, highly branched macromolecules with well-defined structures, have shown promise in various biomedical applications, including imaging and therapy. In the context of prostate cancer, dendrimers offer unique advantages due to their tunable properties, controlled size, and surface functionalities. Here are some ways dendrimers are being explored in imaging and therapy for prostate cancer:

1. Imaging

a. Contrast Agents: Dendrimers can be functionalized with imaging agents such as fluorophores, radioisotopes, or magnetic resonance imaging (MRI) contrast agents. This allows for enhanced imaging capabilities, enabling better visualization of tumors.

b. Multimodal Imaging: Dendrimers can be designed to carry multiple imaging agents simultaneously, enabling multimodal imaging approaches. Combining techniques like MRI, positron emission tomography (PET), and optical imaging enhances diagnostic accuracy.

c. Targeted Imaging: Surface modifications of dendrimers with specific ligands enable targeted imaging of prostate cancer cells. This improves the contrast between cancerous and healthy tissues, reducing false positives and improving overall imaging accuracy.

2. Therapeutic Applications

a. Drug Delivery: Dendrimers can serve as drug delivery vehicles due to their ability to encapsulate and release therapeutic agents in a controlled manner. In prostate cancer, this allows for targeted delivery of chemotherapeutic drugs to the cancer cells while minimizing damage to healthy tissues.

b. Gene Delivery: Dendrimers can be utilized to deliver therapeutic genes, RNA, or other nucleic acids to prostate cancer cells. This opens up possibilities for gene therapy, where specific genes can be introduced to modulate cellular processes or induce apoptosis in cancer cells.

c. Photothermal Therapy: Some dendrimers possess intrinsic properties that make them suitable for photothermal therapy. When exposed to specific wavelengths of light, these dendrimers generate heat, selectively killing cancer cells. This can be a valuable therapeutic option for prostate cancer treatment.

d. Immunotherapy: Dendrimers can be employed in immunotherapeutic approaches by carrying antigens or immunomodulatory agents. This stimulates the immune system to recognize and attack prostate cancer cells, potentially offering a more targeted and durable treatment strategy.

3. Combination Therapies

Dendrimers can be part of combination therapies, where multiple therapeutic modalities are integrated. For example, a dendrimer may carry both an imaging agent for real-time monitoring and a therapeutic payload for simultaneous treatment.

While the potential of dendrimers in prostate cancer imaging and therapy is promising, it's essential to note that research in this field is ongoing, and clinical translation is still in its early stages. Collaborative efforts between researchers, clinicians, and pharmaceutical companies are crucial for advancing dendrimer-based strategies for prostate cancer management.[49,50,51]

4.1 Diagnostic imaging modalities: Using nanoparticles (NPs) to improve cancer detection and therapy, nanotechnology is at the forefront of anticancer medication research. Oncology researchers have looked at nanodrug delivery technologies in depth because of their high demand. Liposomes, polymeric nanoparticles, magnetic nanoparticles, gold nanoparticles, mesoporous silica

nanoparticles, quantum dots, micelles, and dendritic polymers are all examples of common nanocarriers. Indeed, NPs' biological dispersion in vivo is heavily influenced by their size, surface characteristics, and shape.[52] Dendrimers have the potential to be exploited in two main ways for the diagnosis and treatment of cancer and other diseases: (i) passive targeting - nano dimension mediated through EPR (enhanced permeability retention) impact, and (ii) active targeting - nano dimension mediated via chemoattractant effect.[53] There may be more benefits to using active targeting. Prostate-specific membrane antigen (PSMA), folic acid receptor (FR), CD44, and mannose 6-phosphate receptor (M6PR) are all prostate cancer surface targets for a variety of specialized expression agents.[54]

4.2 Dendrimers based contrast agents: The use of contrast agents in magnetic resonance imaging (MRI) allows for more sensitive imaging to be obtained. pictures may either be very bright (T1 weighted pictures) or very dark (T2 weighted images). On the other hand, contrast compounds may be employed to speed up the process, which is helpful in both clinical diagnosis and basic research by decreasing the time it takes for water molecules to move through a fluid. Gadolinium (Gd3+) compounds, which are paramagnetic, are found in the majority of contrast agents used in medicine. In light of these drawbacks, however, work is being done to develop a new generation of Gd-MRI contrast agents that would allow for lower dosage administration without sacrificing sensitivity. As a result, we may see an increasing number of studies on Gd-functionalized dendrimers in scholarly journals. Dendrimers' sensitivity is enhanced by gadolinium-based contrast because an increase in the amount of Gd3+ in the molecule makes it more spherical(55). Additionally, the buildup of contrast agents in the neoplastic tissue has to be monitored. Since tumours often have underdeveloped lymphatic vessels, multiarticulate contrast agents should have a greater propensity to target neoplastic tissues than healthy ones. There are several published accounts of the use of various dendrimers as MRI contrasts.[56]

4.3 Molecular imaging theragnostic: Clinical applications of molecular imaging probes using positron emission tomography/computed tomography (PET/CT) or positron emission tomography/magnetic resonance imaging (PET/MRI) are being made in prostate cancer (PCa) diagnosis and image-guided precision surgery. This article summarizes the rapidly growing list of molecular imaging probes in this field, including their applications in early diagnosis of primary prostate lesions, detection of lymph node, skeletal, and visceral metastases in patients who have biochemical relapsed, and intraoperative guidance for detection of tumour margins and preservation of nerves. Exploration and study in this sector will ultimately lead to higher precision theragnostic of PCa, despite the fact that each imaging probe exhibits preferential effectiveness in certain applications and limits in others.[57]

5. COMBINATION THERAPIES

The use of combination therapy, in which two or more therapeutic medicines are used together, is fundamental in cancer treatment. Combining anti-cancer medications has been shown to be more effective than either using them separately or as monotherapy because of the synergistic or cumulative effects they have on targeting important pathways. This strategy has the potential to lessen medication resistance while simultaneously offering therapeutic anti-cancer effects include slowing tumour development and metastasis, stopping mitotically active cells, decreasing cancer stem cell populations, and triggering apoptosis.

5.1 Dendrimers mediated combination therapy approaches: The combination of paclitaxel (PTX) and alendronate (ALN) was carried via a PEG-dendrimer, H(2)N-PEG-dendrimer-(COOH).[4] For cancer bone metastases, the pharmacokinetic profile of the PTX-PEG-ALN compound was much better than that of the free medicines without any solubilizing agent.[58] Dendritic polymers including proteins, enzymes, and viruses are readily functionalized and offer several benefits, including extended drug life, high stability, water solubility, and lower immunogenicity and antigenicity. Dendrimers are used in medication delivery, gene delivery, magnetic resonance imaging contrast agents, and sensors because of their properties.[59] Passive and/or active targeting techniques might increase target specificity using these dendrimers as carrier molecules. pH-activated polymers were used as a drug-delivery vehicle system with photochemical internalization (PCI) capability to deliver membrane impermeable macromolecules from endocytic vesicles into the cytosol, improving anticancer drug efficacy and reducing side effects. To demonstrate this, DOX was conjugated to polyamidoamine (PAMAM) dendrimers using pH-sensitive and -insensitive linkers and paired with various PCI providers. At higher doses, PCI methods greatly increased free DOX's cytotoxicity on Ca9-22 cells. The "light after" PCI therapy released DOX from PAMAM-hyd-DOX conjugates, causing nuclear accumulation of DOX and cell death via synergistic effects.[60]

5.2 Synergistic effects and improved therapeutic outcomes: A platform for combining medicines with complimentary modes of action is provided by dendrimers. Dendrimers, for instance, may contain medications that block several signaling pathways in cancer cells in cancer treatment. This results in synergistic effects, where a drug's combined activity is more powerful than a drug's individual action. Lower

individual medicine dosages are possible with this strategy, which minimizes negative effects.[61]

1. Multi-Functional Loading: Dendrimers are very adaptable structures that may be designed to transport a range of therapeutic substances. Traditional chemotherapy medications that kill rapidly proliferating cancer cells, targeted treatments that precisely limit the growth pathways of cancer cells, and imaging agents that aid in the visualization of tumour development and therapeutic response are some examples of these agents. Combining these many medicines inside a single dendrimer platform enables the development of a robust and diverse therapeutic strategy that targets cancer cells through several routes.[62]
2. Enhanced Accumulation: Dendrimers may be made to take advantage of the EPR effect, which is a condition in which blood vessels in tumour tissue accumulate nanoparticles like dendrimers due to leaky and irregularly shaped blood vessels. The concentration of therapeutic drugs increases as a consequence of this accumulation, maximizing their efficacy and lowering their exposure to healthy tissues.[63]
3. Combination treatment is made possible by dendrimers' capacity to transport many therapeutic substances. For instance, a dendrimer may include both a targeted treatment that inhibits a particular protein essential for cancer cell viability and a chemotherapy agent that breaks DNA. The medications' individual effectiveness is increased as a result of the combination approach's synergistic impact.[64]

5.3 Overcoming treatment resistant and repalse: Dendrimers are used as carriers to deliver therapeutic drugs to cancer cells while avoiding the processes that cause drug resistance in order to combat multidrug resistance (MDR) in the treatment of prostate cancer using a dendrimer platform. Due to their well-defined structure and capacity to encapsulate a variety of medicines, dendrimers are highly branched, tree-like macromolecules that make good candidates for drug administration. To treat MDR in prostate cancer, a dendrimer platform may be employed in the following ways:
1. Comprehending multidrug resistance (MDR): MDR is the process whereby cancer cells develop a resistance to several drugs. This resistance may develop as a result of a number of factors, including improved DNA repair mechanisms, altered drug metabolism, and drug efflux pumps. Strategies that block these pathways and improve medication delivery to cancer cells are necessary to overcome MDR.[65]
2. Dendrimer Design and Functionalization: Dendrimers have an outside surface that may be changed to include medicines, targeting ligands, and other functional groups. They also include a core, inner branches, and exterior branches. Dendrimers may transport medications and increase their circulation time, selectivity, and absorption by cancer cells by surface functionalization.
3. Drug Loading and Encapsulation: The inside of dendrimers may be used to encapsulate therapeutic substances such as chemotherapeutic medicines, small compounds, nucleic acids, and peptides. The medications are shielded from deterioration, their solubility is improved, and their release is controlled by this encapsulation.[66,67,68]

6. CHALLENGES AND FUTURE PERSPECTIVE

6.1 Preclinical studies and clinical translations: Dendrimers' adaptable chemical makeup allows for a wide range of applications in fields including chemistry, biology, and medicine. One of the most adaptable nanomaterials, dendrimers have been widely characterized as having both medicinal and diagnostic uses. Dendrimers are either used as medications or as possible dendrimers in nanomedicine are their high biocompatibility, good water solubility, and their entry into cells through endocytosis, where they are not typically subject to pump efflux at the cellular membrane. Additionally, only dendrimer nanoparticles may be utilized for active or passive drug targeting and are suited for a wide range of delivery routes, including intravenous, intranasal, transdermal, ocular, and many more.[69] Why aren't dendrimers used in clinical trials with systemic administration despite the plethora of published articles and patents in nanomedicine? Szoka et al. created a similar study for cancer nanomedicine.[70] These researchers emphasized that the vast global budget devoted to nanotechnology research (US $10 billion in 2011) and the number of published articles in the area of cancer nanomedicine are both negatively connected to the number of nanodrugs on the market. The authors presented a dichotomy between the need for academicians to continue publishing and receiving funding for basic science and the need to receive grants for nanocarrier drug formulations to drug approval, which is the goal of pharmaceutical companies, based on the business model of inventors, innovators, and "imitators" (copyists). If we are genuinely interested in getting new pharmaceuticals into the clinic, we should concentrate less on our publishing record and more on developing scientific advancement that translates into patient care, according to a recommendation for three different awards for inventors, innovators, and "imitators." Dendrimers in particular and nanotherapeutic compounds in general should fall under this clause.[71]

6.2 Safety and toxicity consideration: In the area of medication delivery, dendrimers have unquestionably contributed to significant advancements. Regarding their potential in the biomedical field, there is a lot of optimism, but due to their nanometric size, or 1-100 nm, they can interact efficiently and specifically with cellular elements like plasma membranes, cell organelles (endosomes, mitochondria, and nucleus), and proteins like enzymes, all of which are in the nanometer size range.[72] The majority of the nanoparticle varieties that scientists have created are non-selective. The nanoscale size range of nanoparticles allowed them to interact with

or pass through the biological system's plasma membrane. These characteristics of nanocarriers are being developed for in vivo gene transfer and are of great interest in cell transfection strategy.[73] However, these nanoparticles' ability to induce cytotoxicity is another facet of their non-selective absorption. The cytotoxic properties of dendrimers, the mechanism by which these cationic macromolecules cause cytotoxicity, and potential countermeasures to dendrimer toxicity are the main topics of the following section.[74] Despite the fact that dendrimers have several pharmacological and biological uses, their suitability for clinical use is limited by the toxicity associated with their terminal NH2 groups and multiple cationic charges.[75] Conflicting data exist on dendrimer safety. Free amine groups that are present at their peripheral have been reported to be harmful in terms of concentration and production, reported the cytotoxicity of cationic melamine dendrimers with surface groups such amine, guanidine, carboxylate, sulphonate, or phosphonate, and came to the conclusion that these dendrimers were substantially more harmful to cells than anionic or PEG-modified dendrimers. The destabilization of the cell membrane and subsequent cell lysis are caused by cationic macromolecules in general as well as dendrimers. This is a significant discovery that might provide scientists doing related study a piece of advice.[76]

6.3 Regulatory hurdles and commercialization*:* Only a small number of research on non-viral carriers of genetic material and medications have been used in clinical practice, despite an upward trend in the frequency of these studies. A significant portion of research on dendrimers has been conducted over the last two decades, but only a small number of these findings have been used in clinical settings and have gone on to become commercially successful. The fact that just a tiny portion of nano-carriers, particularly dendrimers, were shown to be effective in clinical trials, despite the exponential rise in nanoscience journals and the vast amount of labour required to develop them extensively, is very astounding. It should be emphasized, nevertheless, that this pattern is gradually shifting and that a rising number of pre-clinical research on dendrimers are being approved by the regulatory bodies in charge of overseeing clinical trials.[77] According to a 2018 article about poly-L-lysine dendrimer clinical trials, "ImDendrim" was a dendrimer-based system that sought to transfer the 188Rhenium-ligand (nitro-imidazole-methyl-1,2,3-triazol-methyl- di-[2-pycolyl] amine) for the treatment of colorectal cancer. ImDendrim satisfies required safety and effectiveness requirements, according to an interventional trial including 10 patients with incurable liver cancer who were resistant to conventional chemotherapy.[78] The adoption of clear guidelines allowing for the comparison of any form of dendritic-like nano-system in terms of their physico-chemical characteristics would be made possible by this, allowing for the unification and standardization that is required. On this foundation, a novel nano-framework might be developed to forecast potential interactions between nano systems and the biological environment. A more comprehensive understanding of the effects of dendrimers on cell physiology and a higher likelihood of translation into the clinical stage will be made possible by the presence of such a generalized structural-functional framework, which will enable the greatest possible reduction in the number of variables used to describe nano-systems.[79]

6.4 Emerging trends and future direction: Due to the many benefits in the areas of drug delivery, diagnostics, and treatment, research on dendrimer-based nanomedicines for prostate cancer has drawn a lot of interest.[80] It is predicted that additional products will soon enter clinical trials thanks to significant advancements in dendrimer-based nanomedicines. Dendrimers as cancer nanotherapeutics have, however, shown a few difficulties that will need to be resolved in further research. To prevent unintended nanocarrier toxicity to healthy cells, analytical characterization and manufacturing of dendrimers conjugated with ligands or medications should be carried out with care.[81] Additionally, there are difficulties in commercializing nanomedicine, such as lags in clinical translation.[82] The issues to be resolved include the absence of in vitro-in vivo drug release profile correlation as well as a thorough understanding of nano-bio interfacial interactions. Additionally, because the physicochemical qualities might change from batch to batch, the large-scale manufacture of dendrimers and products comprising several procedures is a difficulty. Consequently, dendrimers must be stable and reproducible. Despite the challenges, the use of dendrimers in medication delivery, diagnostics, and treatment holds great promise for creating more effective management plans for prostate cancer. At this point, it is conceivable that future advances in dendrimers via smart design may result in a considerable advancement in anticancer treatment, improving patient results.[83]

CONCLUSION

In conclusion, cancer may be fatal when it begins to infect important bodily organs like the liver, lung, or brain, as well as their nerves, blood vessels, and capacity for regular operation. Therefore, for an early, immediate identification as well as prognosis of prostate cancer, an adequate and complete diagnostic, targeting, and therapeutic strategy is in fact necessary. Prostate cancer is often treatable when caught in its early stages with an appropriate screening approach. As a result, as compared to other cancer types, the typical long-term prognosis for prostate cancer is quite positive. The negative effects of standard prostate cancer treatments must always be managed with extra therapy. As a result, research is being done to create chemotherapy that is more physiologically tolerable, stable, on-target, and efficacious while having a lower adverse effect profile. By creating diverse categories and functionalities of nanoplatforms, nanotechnology has now significantly

advanced the science of cancer. It has unique properties that enable it to deliver medications to certain, targeted malignant cells, minimizing harm to other healthy cells in the body. Additionally, these nanoplatforms' imaging capabilities offer ongoing therapeutic monitoring that makes it easier to detect cancer cells, administer treatment quickly, deliver image-guided focal therapy, track drug delivery and distribution, predict treatment outcomes, and stratify patients. Dendrimers, one of the NPs in cancer chemotherapy that are the subject of the greatest research, are receiving increasing attention as a result of a few instances where they have been helpful in treating certain tumours. It uses improved medication delivery while also avoiding biological problems that standard prostate cancer treatment runs into. It may be specifically designed as a drug carrier with low toxicity and precisely regulated drug release for therapeutic, targeted, and imaging applications by modifying its size, shape, and surface morphology. Consequently, it has the potential to manage cancer as a theragnostic platform.

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REFERENCES

1. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature, 2007; 449: 419–26. https://doi.org/10.1038/nature06175.
2. Bhattacharya S, Kuwar UC. Dendrimer evolution timeline: Ground-breaking progress in cancer treatment. Indian Journal of Pharmacy and Pharmacology, 2021; 8: 179–81. https://doi.org/10.18231/j.ijpp.2021.030.
3. Miller LL, Duan RG, Tully DC, Tomalia DA. Electrically Conducting Dendrimers. Journal of the American Chemical Society, 1997; 119: 1005–10. https://doi.org/10.1021/ja963270j.
4. Moradi M, Abdolhosseini M, Zarrabi A, johari B. A review on application of Nano-structures and Nano-objects with high potential for managing different aspects of bone malignancies. Nano-Structures & Nano-Objects, 2019; 19: 100348. https://doi.org/10.1016/j.nanoso.2019.100348.
5. Yadav R, Balasubramanian K. Polyacrylonitrile/Syzygium aromaticum hierarchical hydrophilic nanocomposite as a carrier for antibacterial drug delivery systems. RSC Advances, 2015; 5: 3291–8. https://doi.org/10.1039/c4ra12755b.
6. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell, 2011; 144: 646–74. https://doi.org/10.1016/j.cell.2011.02.013.
7. Chiangjong W, Chutipongtanate S, Hongeng S. Anticancer peptide: Physicochemical property, functional aspect and trend in clinical application (Review). International Journal of Oncology, 2020; 57: 678–96. https://doi.org/10.3892/ijo.2020.5099.
8. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 2021; 71: 209–49. https://doi.org/10.3322/caac.21660.
9. Zhu Y, Mo M, Wei Y, Wu J, Pan J, Freedland SJ, et al. Epidemiology and genomics of prostate cancer in Asian men. Nature Reviews Urology, 2021; 18: 282–301. https://doi.org/10.1038/s41585-021-00442-8.
10. Gupta S, Gupta PK, Dharanivasan G, Verma RS. Current prospects and challenges of nanomedicine delivery in prostate cancer therapy. Nanomedicine, 2017; 12: 2675–92. https://doi.org/10.2217/nnm-2017-0236.
11. Hyde MK, Opozda M, Laurie K, Vincent AD, Oliffe JL, Nelson CJ, et al. Men's sexual help-seeking and care needs after radical prostatectomy or other non-hormonal, active prostate cancer treatments. Supportive Care in Cancer, 2020; 29: 2699–711. https://doi.org/10.1007/s00520-020-05775-5.
12. Updates to the National Cancer Institute's PDQ Information from Recently Published Oncology Research. JNCI: Journal of the National Cancer Institute, 2017; 109. https://doi.org/10.1093/jnci/djx274.
13. Parveen S, Misra R, Sahoo SK. Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine: Nanotechnology, Biology and Medicine, 2012; 8: 147–66. https://doi.org/10.1016/j.nano.2011.05.016.
14. Wolin SL, Maquat LE. Cellular RNA surveillance in health and disease. Science, 2019; 366: 822–7. https://doi.org/10.1126/science.aax2957.
15. Dayyani N, Khoee S, Ramazani A. Design and synthesis of pH-sensitive polyamino-ester magneto-dendrimers: Surface functional groups effect on viability of human prostate carcinoma cell lines DU145. European Journal of Medicinal Chemistry, 2015; 98: 190–202. https://doi.org/10.1016/j.ejmech.2015.05.028.
16. Sanz del Olmo N, Maroto-Diaz M, Quintana S, Gómez R, Holota M, Ionov M, et al. Heterofunctional ruthenium(II) carbosilane dendrons, a new class of dendritic molecules to fight against prostate cancer. European Journal of Medicinal Chemistry, 2020; 207: 112695. https://doi.org/10.1016/j.ejmech.2020.112695.
17. Xiong L, Li Z, Li G, Ju H. A DNA dendrimer amplified electrochemical immunosensing method for highly sensitive detection of prostate specific antigen. Analytica Chimica Acta, 2021; 1186: 339083. https://doi.org/10.1016/j.aca.2021.339083.

18. Kavosi B, Navaee A, Salimi A. Amplified fluorescence resonance energy transfer sensing of prostate specific antigen based on aggregation of CdTe QDs/antibody and aptamer decorated of AuNPs-PAMAM dendrimer. Journal of Luminescence, 2018; 204: 368–74. https://doi.org/10.1016/j.jlumin.2018.08.012.
19. Photoresponsive Arylether Dendrimers with Azobenzene Core and Terminal Vinyl Groups. Bulletin of the Korean Chemical Society, 2008; 29: 761–6. https://doi.org/10.5012/bkcs.2008.29.4.761.
20. Hawker CJ, Frechet JMJ. Control of surface functionality in the synthesis of dendritic macromolecules using the convergent-growth approach. Macromolecules, 1990; 23: 4726–9. https://doi.org/10.1021/ma00223a036.
21. Khodadust R, Mutlu P, Yalcın S, Unsoy G, Gunduz U. Polyinosinic:polycytidylic acid loading onto different generations of PAMAM dendrimer-coated magnetic nanoparticles. Journal of Nanoparticle Research, 2013; 15. https://doi.org/10.1007/s11051-013-1860-6.
22. Mousa S, Bharali D, Khalil M, Gurbuz M, Simone. Nanoparticles and cancer therapy: A concise review with emphasis on dendrimers. International Journal of Nanomedicine, 2009; 1. https://doi.org/10.2147/ijn.s4241.
23. Bharali DJ, Yalcin M, Davis PJ, Mousa SA. Tetraiodothyroacetic acid-conjugated PLGA nanoparticles: a nanomedicine approach to treat drug-resistant breast cancer. Nanomedicine, 2013; 8: 1943–54. https://doi.org/10.2217/nnm.12.200.
24. GILLIES E, FRECHET J. Dendrimers and dendritic polymers in drug delivery. Drug Discovery Today, 2005; 10: 35–43. https://doi.org/10.1016/s1359-6446(04)03276-3.
25. Pérez-Ferreiro M, M. Abelairas A, Criado A, Gómez IJ, Mosquera J. Dendrimers: Exploring Their Wide Structural Variety and Applications. Polymers, 2023; 15: 4369. https://doi.org/10.3390/polym15224369.
26. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, et al. Dendrimers: synthesis, applications, and properties. Nanoscale Research Letters, 2014; 9. https://doi.org/10.1186/1556-276x-9-247.
27. Butowska K, Han X, Gong N, El-Mayta R, Haley RM, Xue L, et al. Doxorubicin-conjugated siRNA lipid nanoparticles for combination cancer therapy. Acta Pharmaceutica Sinica B., 2023; 13: 1429–37. https://doi.org/10.1016/j.apsb.2022.07.011.
28. Meher N, VanBrocklin HF, Wilson DM, Flavell RR. PSMA-Targeted Nanotheranostics for Imaging and Radiotherapy of Prostate Cancer. Pharmaceuticals, 2023; 16: 315. https://doi.org/10.3390/ph16020315.
29. Luo D, Wang X, Ramamurthy G, Walker E, Zhang L, Shirke A, et al. Evaluation of a photodynamic therapy agent using a canine prostate cancer model. The Prostate, 2023; 83: 1176–85. https://doi.org/10.1002/pros.24560.
30. Kumar P, Mishra B. Colon Targeted Drug Delivery Systems -An Overview. Current Drug Delivery, 2008; 5: 186–98. https://doi.org/10.2174/156720108784911712.
31. Tiwari G, Tiwari R, Bannerjee S, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: An updated review. International Journal of Pharmaceutical Investigation, 2012; 2: 2. https://doi.org/10.4103/2230-973x.96920.
32. Ravichandran R. Studies on Dissolution Behaviour of Nanoparticulate Curcumin Formulation. Advances in Nanoparticles, 2013; 02: 51–9. https://doi.org/10.4236/anp.2013.21010.
33. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. Drug Discovery Today, 2012; 17: 1044–52. https://doi.org/10.1016/j.drudis.2012.05.010.
34. Hema S, Thambiraj S, Shankaran DR. Nanoformulations for Targeted Drug Delivery to Prostate Cancer: An Overview. Journal of Nanoscience and Nanotechnology, 2018; 18: 5171–91. https://doi.org/10.1166/jnn.2018.15420.
35. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. Drug Discovery Today, 2012; 17: 1044–52. https://doi.org/10.1016/j.drudis.2012.05.010.
36. Wang AZ, Langer R, Farokhzad OC. Nanoparticle Delivery of Cancer Drugs. Annual Review of Medicine, 2012; 63: 185–98. https://doi.org/10.1146/annurev-med-040210-162544.
37. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Advanced Drug Delivery Reviews, 2014; 66: 2–25. https://doi.org/10.1016/j.addr.2013.11.009.
38. Biswas S, Torchilin VP. Nanopreparations for organelle-specific delivery in cancer. Advanced Drug Delivery Reviews, 2014; 66: 26–41. https://doi.org/10.1016/j.addr.2013.11.004.
39. Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. Advanced Drug Delivery Reviews, 2011; 63: 131–5. https://doi.org/10.1016/j.addr.2010.03.011.
40. Maruyama K. Intracellular targeting delivery of liposomal drugs to solid tumors based on EPR effects. Advanced Drug Delivery Reviews, 2011; 63: 161–9. https://doi.org/10.1016/j.addr.2010.09.003.
41. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology, 2007; 2: 751–60. https://doi.org/10.1038/nnano.2007.387.
42. Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta Biochimica Polonica, 2001; 48: 199–208. https://doi.org/10.18388/abp.2001_5127.

43. Lin Q, Jiang G, Tong K. Dendrimers in Drug-Delivery Applications. Designed Monomers and Polymers, 2010; 13: 301–24. https://doi.org/10.1163/138577210x509552.
44. Suganya V, Anuradha V. Microencapsulation and Nanoencapsulation: A Review. International Journal of Pharmaceutical and Clinical Research, 2017; 9. https://doi.org/10.25258/ijpcr.v9i3.8324.
45. Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nature Reviews Drug Discovery, 2011; 10: 417–27. https://doi.org/10.1038/nrd3455.
46. Tredan O, Galmarini CM, Patel K, Tannock IF. Drug Resistance and the Solid Tumor Microenvironment. JNCI Journal of the National Cancer Institute, 2007; 99: 1441–54. https://doi.org/10.1093/jnci/djm135.
47. Lespine A, Ménez C, Bourguinat C, Prichard RK. P-glycoproteins and other multidrug resistance transporters in the pharmacology of anthelmintics: Prospects for reversing transport-dependent anthelmintic resistance. International Journal for Parasitology: Drugs and Drug Resistance, 2012; 2: 58–75. https://doi.org/10.1016/j.ijpddr.2011.10.001.
48. Booser DJ, Hortobagyi GN. Anthracycline Antibiotics in Cancer Therapy. Drugs, 1994; 47: 223–58. https://doi.org/10.2165/00003495-199447020-00002.
49. Bennett KM, Jo J, Cabral H, Bakalova R, Aoki I. MR imaging techniques for nano-pathophysiology and theranostics. Advanced Drug Delivery Reviews, 2014; 74: 75–94. https://doi.org/10.1016/j.addr.2014.04.007.
50. Siddique S, Chow JCL. Application of Nanomaterials in Biomedical Imaging and Cancer Therapy. Nanomaterials, 2020; 10: 1700. https://doi.org/10.3390/nano10091700.
51. Longmire M, Choyke P, Kobayashi H. Dendrimer-Based Contrast Agents for Molecular Imaging. Current Topics in Medicinal Chemistry, 2008; 8: 1180–6. https://doi.org/10.2174/156802608785849021.
52. Ahmed A, Sarwar S, Hu Y, Munir MU, Nisar MF, Ikram F, et al. Surface-modified polymeric nanoparticles for drug delivery to cancer cells. Expert Opinion on Drug Delivery, 2020; 18: 1–24. https://doi.org/10.1080/17425247.2020.1822321.
53. Nishiyama N, Koizumi F, Okazaki S, Matsumura Y, Nishio K, Kataoka K. Differential Gene Expression Profile between PC-14 Cells Treated with Free Cisplatin and Cisplatin-Incorporated Polymeric Micelles. Bioconjugate Chemistry, 2003; 14: 449–57. https://doi.org/10.1021/bc025555t.
54. Lakshmanan V-K. Therapeutic efficacy of nanomedicines for prostate cancer: An update. Investigative and Clinical Urology, 2016; 57: 21. https://doi.org/10.4111/icu.2016.57.1.21.
55. Caravan P. Strategies for increasing the sensitivity of gadolinium based MRI contrast agents. Chemical Society Reviews, 2006; 35: 512. https://doi.org/10.1039/b510982p.
56. McMahon MT, Bulte JWM. Two decades of dendrimers as versatile MRI agents: a tale with and without metals. WIREs Nanomedicine and Nanobiotechnology, 2017; 10. https://doi.org/10.1002/wnan.1496.
57. Tan Y, Fang Z, Tang Y, Liu K, Zhao H. Clinical advancement of precision theranostics in prostate cancer. Frontiers in Oncology, 2023; 13. https://doi.org/10.3389/fonc.2023.1072510.
58. Clementi C, Miller K, Mero A, Satchi-Fainaro R, Pasut G. Dendritic Poly(ethylene glycol) Bearing Paclitaxel and Alendronate for Targeting Bone Neoplasms. Molecular Pharmaceutics, 2011; 8: 1063–72. https://doi.org/10.1021/mp2001445.
59. Patel A, Patel V, Patel A, Dave J, Patel C. Determination of galantamine hydrobromide in bulk drug and pharmaceutical dosage form by spectrofluorimetry. Journal of Pharmacy And Bioallied Sciences, 2013; 5: 314. https://doi.org/10.4103/0975-7406.120079.
60. Lai P-S, Lou P-J, Peng C-L, Pai C-L, Yen W-N, Huang M-Y, et al. Doxorubicin delivery by polyamidoamine dendrimer conjugation and photochemical internalization for cancer therapy. Journal of Controlled Release, 2007; 122: 39–46. https://doi.org/10.1016/j.jconrel.2007.06.012.
61. Lee JH, Nan A. Combination Drug Delivery Approaches in Metastatic Breast Cancer. Journal of Drug Delivery, 2012; 2012: 1–17. https://doi.org/10.1155/2012/915375.
62. Kaurav M, Ruhi S, Al-Goshae HA, Jeppu AK, Ramachandran D, Sahu RK, et al. Dendrimer: An update on recent developments and future opportunities for the brain tumors diagnosis and treatment. Frontiers in Pharmacology, 2023; 14. https://doi.org/10.3389/fphar.2023.1159131.
63. Hsu C-Y, Rheima AM, Kadhim MM, Ahmed NN, Mohammed SH, Abbas FH, et al. An overview of nanoparticles in drug delivery: Properties and applications. South African Journal of Chemical Engineering, 2023; 46: 233–70. https://doi.org/10.1016/j.sajce.2023.08.009.
64. Gholap AD, Bhowmik DD, Deshmukh AY, Hatvate NT. Quintessential impact of dendrimer bioconjugates in targeted drug delivery. Bioconjugated Materials Part 2 Applications in Drug Delivery, Vaccine Formulations and Important Conjugates for Cancer Therapy, 2023; 257–302. https://doi.org/10.1016/bs.coac.2023.02.009.
65. Huang S, Huang X, Yan H. Peptide dendrimers as potentiators of conventional chemotherapy in the treatment of pancreatic cancer in a mouse model. European Journal of Pharmaceutics and Biopharmaceutics, 2022; 170: 121–32. https://doi.org/10.1016/j.ejpb.2021.11.005.
66. Sandoval-Yañez C, Castro Rodriguez C. Dendrimers: Amazing Platforms for Bioactive

Molecule Delivery Systems. Materials, 2020; 13: 570. https://doi.org/10.3390/ma13030570.
67. Mittal P, Saharan A, Verma R, Altalbawy FMA, Alfaidi MA, Batiha GE-S, et al. Dendrimers: A New Race of Pharmaceutical Nanocarriers. BioMed Research International, 2021; 2021: 1–11. https://doi.org/10.1155/2021/8844030.
68. Mignani S, Rodrigues J, Tomas H, Roy R, Shi X, Majoral J-P. Bench-to-bedside translation of dendrimers: Reality or utopia? A concise analysis. Advanced Drug Delivery Reviews, 2018; 136–137: 73–81. https://doi.org/10.1016/j.addr.2017.11.007.
69. DUNCAN R, IZZO L. Dendrimer biocompatibility and toxicity. Advanced Drug Delivery Reviews, 2005; 57: 2215–37. https://doi.org/10.1016/j.addr.2005.09.019.
70. Venditto VJ, Szoka FC. Cancer nanomedicines: So many papers and so few drugs! Advanced Drug Delivery Reviews, 2013; 65: 80–8. https://doi.org/10.1016/j.addr.2012.09.038.
71. Mignani S, Shi X, Rodrigues J, Roy R, Muñoz-Fernández Á, Ceña V, et al. Dendrimers toward Translational Nanotherapeutics: Concise Key Step Analysis. Bioconjugate Chemistry, 2020; 31: 2060–71. https://doi.org/10.1021/acs.bioconjchem.0c00395.
72. Park H-H, Lee S, Son H-Y, Park S-B, Kim M-S, Choi E-J, et al. Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. Archives of Pharmacal Research, 2008; 31: 1303–11. https://doi.org/10.1007/s12272-001-2110-5.
73. Gan X, Cai Y, Choi C, Ma Z, Chen J, Li B. Potential impacts of invasive Spartina alterniflora on spring bird communities at Chongming Dongtan, a Chinese wetland of international importance. Estuarine, Coastal and Shelf Science, 2009; 83: 211–8. https://doi.org/10.1016/j.ecss.2009.03.026.
74. Jain K, Kesharwani P, Gupta U, Jain NK. Dendrimer toxicity: Let's meet the challenge. International Journal of Pharmaceutics, 2010; 394: 122–42. https://doi.org/10.1016/j.ijpharm.2010.04.027.
75. Agashe HB, Dutta T, Garg M, Jain NK. Investigations on the toxicological profile of functionalized fifth-generation poly(propylene imine) dendrimer. Journal of Pharmacy and Pharmacology, 2006; 58: 1491–8. https://doi.org/10.1211/jpp.58.11.0010.
76. Chen D, Zhao M, Mundy GR. Bone Morphogenetic Proteins. Growth Factors, 2004; 22: 233–41. https://doi.org/10.1080/08977190412331279890.
77. Tarach P, Janaszewska A. Recent Advances in Preclinical Research Using PAMAM Dendrimers for Cancer Gene Therapy. International Journal of Molecular Sciences, 2021; 22: 2912. https://doi.org/10.3390/ijms22062912.
78. Belhadj-Tahar H, Chen A, Jia Y, Wu S, Sadeg N, Zhao H, et al. In situ anti-cancer agent derived from [188re]rhenium nitro-imidazole ligand loaded poly-l-lysine dendrimer administrated by direct CT guided stereotactic intrahepatic injection. Journal of Clinical Oncology, 2018; 36: e15569–e15569. https://doi.org/10.1200/jco.2018.36.15_suppl.e15569.
79. Mignani S, El Kazzouli S, Bousmina M, Majoral J-P. Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: A concise overview. Advanced Drug Delivery Reviews, 2013; 65: 1316–30. https://doi.org/10.1016/j.addr.2013.01.001.
80. Navya PN, Kaphle A, Srinivas SP, Bhargava SK, Rotello VM, Daima HK. Current trends and challenges in cancer management and therapy using designer nanomaterials. Nano Convergence, 2019; 6. https://doi.org/10.1186/s40580-019-0193-2.
81. Navya PN, Daima HK. Rational engineering of physicochemical properties of nanomaterials for biomedical applications with nanotoxicological perspectives. Nano Convergence, 2015; 2. https://doi.org/10.1186/s40580-015-0057-3.
82. Nikzamir M, Hanifehpour Y, Akbarzadeh A, Panahi Y. Applications of Dendrimers in Nanomedicine and Drug Delivery: A Review. Journal of Inorganic and Organometallic Polymers and Materials, 2021; 31: 2246–61. https://doi.org/10.1007/s10904-021-01925-2.
83. Nikzamir M, Akbarzadeh A, Panahi Y. An overview on nanoparticles used in biomedicine and their cytotoxicity. Journal of Drug Delivery Science and Technology, 2021; 61: 102316. https://doi.org/10.1016/j.jddst.2020.102316.