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Dendrimers: A Versatile and Transformative Platform in Biomedicine

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Abstract

Dendrimers have emerged as one of the most promising nanotechnological platforms in modern biomedicine, owing to their precise molecular architecture, multivalency, and customizable surface chemistry. These characteristics enable dendrimers to address complex biomedical challenges with a level of control and specificity that traditional materials often lack. Dendrimers have enabled breakthroughs in drug, vaccine, and gene delivery, diagnostics, and tissue engineering. This review highlights their key biomedical applications and future potential.

Keywords: Dendrimers; Antimicrobial; Non-viral gene delivery; Diagnostics

Introduction to Dendrimers

Dendrimers are a unique class of synthetic macromolecules distinguished by their highly branched, tree-like architecture [1-5]. Structurally, they consist of three key components: a central core, multiple layers of repeating branching units known as generations, and numerous terminal functional groups on the periphery. This meticulously organized structure results in a spherical, nanoscale molecule with exceptional uniformity and symmetry. Unlike conventional linear polymers, dendrimers exhibit monodispersity, meaning they possess a consistent molecular weight and size across a batch, which is critical for reproducibility in biomedical applications. The presence of multiple reactive surface groups enables multivalent and robust interactions with various biological targets, enhancing their functionality in complex biological environments [6]. The precise molecular architecture of dendrimers allows for fine-tuning of their physical and chemical properties, such as solubility, surface charge, and biocompatibility. This tunability makes them ideal candidates for a wide range of biomedical applications [7], including targeted drug delivery [7-9], gene therapy, diagnostic imaging [8,10], and tissue engineering [11]. Their internal cavities can encapsulate therapeutic agents, while their surface can be engineered to interact selectively with cells, tissues, or biomolecules. In essence, dendrimers represent a versatile and powerful platform in nanomedicine, offering solutions that traditional polymers cannot match due to their structural limitations [12]. Their ability to combine functionality, precision, and adaptability positions them at the forefront of innovation in biomedical science [8,13].

Dendrimers as Drug Delivery Systems

One of the most prominent and extensively researched biomedical applications of dendrimers is in targeted drug delivery [7-9]. Their unique nanoscale architecture enables

them to act as highly efficient carriers for therapeutic agents. At the molecular level, dendrimers possess internal cavities that can encapsulate hydrophobic drugs [14], protecting them from premature degradation and improving their solubility in aqueous environments. This is particularly valuable for drugs that are poorly water-soluble, as dendrimers can enhance their bioavailability and facilitate their transport across biological membranes. Simultaneously, the surface functional groups of dendrimers can be chemically modified to attach targeting ligands such as antibodies, peptides, carbohydrates, or small molecules [15]. These ligands enable site-specific delivery, allowing dendrimers to recognize and bind to receptors overexpressed on diseased cells such as cancer cells, while sparing healthy tissues. This targeted approach not only improves therapeutic efficacy but also minimizes off-target effects and reduces systemic toxicity [8].

Moreover, dendrimers can be engineered to respond to specific physiological stimuli including pH, temperature, or enzymatic activity. Hence, they can allow controlled and sustained release [7,16] of the drug payload. This feature is particularly advantageous in chronic disease management, where maintaining therapeutic levels over extended periods is crucial. A well-known example of dendrimer-based drug delivery involves poly(amidoamine) (PAMAM) dendrimers, which have been widely studied for their biocompatibility and versatility. PAMAM dendrimers have been successfully used to deliver anticancer agents like methotrexate and doxorubicin, demonstrating enhanced cellular uptake, improved pharmacokinetics, and reduced side effects compared to conventional formulations [15]. In preclinical studies, PAMAM-drug conjugates have shown promising results in targeting tumor cells [17] while minimizing damage to surrounding healthy tissues.

Other dendrimer types, such as polypropylene imine (PPI) and polyester dendrimers, are also being explored for their biodegradability and lower toxicity profiles. In addition, recent studies comprised multifunctional dendrimers that have been used to combine different therapeutic agents with imaging molecules for theragnostic applications. Moreover, that can be built into hybrid systems integrated into liposomes or hydrogels for enhanced delivery and stability [18]. However, despite their promise, dendrimers still face hurdles. Therefore, issues such as cytotoxicity especially in higher generations, have to be overcome. Fortunately, this can be mitigated by PEGylation, glycosylation, or acetylation. Additionally, their complex multi-step syntheses require precise control over branching and purity. Importantly regulatory barriers have recently been achieved since a few dendrimer-based drugs have reached clinical approval [13].

In summary, dendrimers offer a multifaceted platform for drug delivery by combining encapsulation, targeting, and controlled release capabilities. Their adaptability and precision make them ideal candidates for next-generation therapeutics, particularly in oncology, infectious diseases, and neurological disorders.

Dendrimers as Non-Viral Vectors for Gene Delivery

Dendrimers have emerged as a powerful class of non-viral vectors for gene delivery, offering a safer and more controllable alternative to traditional viral-based systems. Their well-defined, branched architecture and tunable surface chemistry make them ideal candidates for transporting genetic material into cells. The gene delivery process using dendrimers relies on their cationic (positively charged) surface groups, which can electrostatically bind to the negatively charged phosphate backbone of nucleic acids such as DNA, siRNA, or mRNA [19,20]. This interaction leads to the formation of stable dendrimer–nucleic acid complexes, often referred to as "dendriplexes." These dendriplexes serve multiple functions that include: condensation of genetic material into nanoscale particles suitable for cellular uptake; protection of nucleic acids from enzymatic degradation by nucleases in the extracellular environment; facilitation of endocytosis, enabling the complex to enter target cells; and endosomal escape, often aided by the "proton sponge effect," allowing the genetic cargo to reach the cytoplasm or nucleus [21].

Numerous studies have demonstrated the efficacy of dendrimers in delivering various forms of genetic material. For instance, dendrimers have been used to silence oncogenes in cancer cells, leading to reduced tumor growth in preclinical models using siRNA delivery. Successful transfection has been observed in both in vitro and in vivo systems, with applications in gene replacement therapy and vaccine development using appropriate plasmid DNA delivery. Emerging research explores dendrimers as carriers for CRISPR-based gene editing tools, offering precise genome modification with reduced immunogenicity by CRISPR/Cas9 components.

Among dendrimers, polyamidoamine (PAMAM) and polypropylene imine (PPI) dendrimers are the most widely studied for gene delivery due to their high transfection efficiency and modifiable surface groups [20,22]. Surface modifications—such as PEGylation or conjugation with targeting ligands-can further enhance biocompatibility, reduce cytotoxicity, and improve tissue-specific delivery [20]. These commercially available dendrimers possess several advantages over viral vectors including: lower immunogenicity; scalability and reproducibility; customizability.

Despite their promise, dendrimer-based gene delivery systems face several challenges. Given that most efficient cationic dendriplexes are especially toxic at higher generations or concentrations, surface group engineering has to be meticulously addressed. Furthermore, endosomal escape still remains a bottleneck for many dendrimer systems. In vivo stability and targeting also necessitate further optimization for clinical translation. Actually, ongoing research focuses on developing biodegradable dendrimers, stimuli-responsive systems, and multifunctional platforms that combine gene delivery with imaging or therapeutic agents.

Dendrimers in Diagnostic Imaging

Dendrimers have gained significant attention in the field of medical diagnostics, particularly as contrast agents in imaging modalities such as magnetic resonance imaging (MRI) [23] and computed tomography (CT) [24]. Their highly branched, nanoscale

architecture and multivalent surface chemistry make them ideal carriers for high-density imaging moieties, enabling enhanced visualization of tissues and pathological conditions.

Dendrimers have been shown to function as contrast agents by encapsulating or conjugating imaging molecules (e.g., gadolinium, iodine, fluorophores) within their internal cavities or on their surface. They also showed improved biodistribution and retention time in target tissues due to their size and surface modifications. Dendrimers can enhance signal intensity and resolution by delivering a higher payload of contrast agents per molecule compared to conventional carriers. Again, their multivalency allows dendrimers to carry multiple imaging units simultaneously, which amplifies the signal and improves the specificity of detection. Additionally, dendrimers can be functionalized with targeting ligands (e.g., antibodies, peptides, carbohydrates) to direct them to specific tissues or disease markers, such as tumors or inflamed regions.

One of the most successful applications of dendrimers in imaging is their use as carriers for gadolinium (Gd^{3+}), a paramagnetic ion commonly used in MRI contrast agents. Free gadolinium is toxic, but when chelated and encapsulated within dendrimers, it becomes safer and more effective [10]. For instance, PAMAM dendrimers conjugated with gadolinium chelates [25] (e.g., DTPA or DOTA) have demonstrated higher relaxivity (signal enhancement) than conventional Gd-based agents; longer circulation times, allowing for extended imaging windows; reduced renal clearance, which is beneficial for imaging vascular structures and tumors. These dendrimer-based agents have shown promise in detecting brain tumors, cardiovascular abnormalities, and lymph node metastases with greater clarity and precision.

Beyond MRI, dendrimers are being explored in CT; optical; and PET and SPECT imaging. In CT imaging, dendrimers conjugated with iodine-based agents improve X-ray attenuation and image contrast [24]. For optical imaging, fluorescent dendrimers enable real-time tracking of cellular processes and tumor localization. Finally, for PET and SPECT, radiolabeled dendrimers (e.g., with 64Cu or 99mTc) offer high-resolution functional imaging for cancer and neurological disorders.

Dendrimers are also being developed as theranostic platforms, combining diagnostic imaging with therapeutic delivery. For example, a dendrimer can simultaneously carry a chemotherapeutic drug and a fluorescent marker, enabling real-time monitoring of drug distribution and efficacy.

Dendrimers in Antimicrobial and Antiviral Applications

Dendrimers have demonstrated significant potential as antimicrobial and antiviral agents, owing to their unique physicochemical properties and customizable surface functionalities [26]. Their intrinsic antimicrobial activity [27] stems primarily from their cationic surface charge, which qualifies them to interact with and disrupt microbial membranes, leading to cell lysis and death [27,28]. The antimicrobial efficacy of dendrimers is largely attributed to electrostatic interactions because the positively charged dendrimers bind to negatively charged microbial cell membranes, destabilizing membrane integrity [29]. Dendrimers can also work through their capacity for membrane disruption that can lead to pore formation, leakage of cellular contents, and eventual cell death. Moreover, they have been shown to inhibit viral replication. For example, dendrimers can interfere with viral attachment, fusion, and replication processes [30]. These mechanisms are effective against a broad spectrum of pathogens, including Gram-positive and Gram-negative bacteria, fungi, and enveloped viruses.

Dendrimers have been additionally explored as topical agents in formulations such as gels, creams, and sprays for treating skin infections, wounds, and mucosal surfaces. Their ability to penetrate biofilms and deliver antimicrobial agents directly to the site of infection enhances their therapeutic potential. In fact, peptide dendrimers can mimic natural antimicrobial peptides and show potent activity against resistant bacterial strains. Silver-dendrimer composites combine the antimicrobial properties of silver ions with the delivery efficiency of dendrimers.

One of the most notable successes in dendrimer-based antiviral therapy is the development of dendrimer-based microbicides for the prevention of sexually transmitted infections, particularly HIV. The first successful application of dendrimers resulted from VivaGel® (SPL7013) which is a poly-L-lysine based dendrimer used as antiviral gel developed by Starpharma [30]. It contains a polyanionic dendrimer that binds to viral envelope proteins, blocking HIV and HSV (herpes simplex virus) from attaching to host cells [30]. Clinical trials have shown that VivaGel® is safe, well-tolerated, and effective in reducing viral transmission risk when applied to vaginal or rectal mucosa. Beyond HIV, dendrimers are being investigated for their ability to inhibit other viruses such as influenza, Zika, and SARS-CoV-2, by targeting viral entry mechanisms or enhancing immune responses.

Dendrimers in Scaffold Design for Tissue Engineering

Tissue engineering aims to restore or replace damaged tissues by combining biomaterials, cells, and bioactive molecules. Among various nanomaterials, dendrimers stand out for their highly branched architecture, multivalency, and customizable surface functionalities, which make them excellent components for scaffold design [1,11]. The capacity to customize surface chemistry can be utilized to enhance cell interaction, bind growth factors, or control degradation rates. Many dendrimers, such as PAMAM and polyester-based types, are biocompatible and can be engineered to degrade safely within the body. One key feature relies on their ability to mimic the extracellular matrix (ECM) through their nanoscale size and branching structure which allow dendrimers to emulate the ECM, thus providing a supportive environment for cell attachment and signaling. This has been particularly effective for glycodendrimers exposing lactoside as surface groups [31].

Dendrimers incorporated into scaffolds have shown to promote cell adhesion by presenting bioactive ligands or peptides on their surface. They can also enhance cell proliferation through controlled release of growth factors or nutrients. Additionally, they can induce differentiation of stem cells into specialized cell types, such as osteoblasts for bone or chondrocytes for cartilage. These properties make dendrimer-based scaffolds suitable for regenerating bone [32], cartilage [33], skin, corneal tissue, and even neural tissue.

Dendrimers are used in various scaffold formats including: hydrogels [34-36] since dendrimers crosslinked with polymers form soft, hydrated networks ideal for skin and cartilage regeneration. Electrospun dendrimer-polymer blends mimic the fibrous structure of native tissues by forming nanofibers. Using porous 3D scaffolds, dendrimers enhance mechanical strength and bioactivity in porous constructs for bone tissue engineering [32]. Through these formulations, dendrimers have been successfully used in corneal wound healing [37], where their surface chemistry supports epithelial cell migration and repair. They have also been used in bone regeneration by demonstrating improved mineralization and osteogenic differentiation. Overall, several studies showed that dendrimers can outperform other nanocarriers like liposomes and nanoemulsions in scaffold integration due to their precise control over surface charge and crosslinking.

Conclusion

Dendrimers represent a versatile and powerful platform in biomedicine, offering multifaceted solutions across key domains such as drug delivery, diagnostics, gene therapy, and tissue engineering. Their unique architecture, characterized by a highly branched, nanoscale structure, enables precise control over size, shape, surface functionality, and molecular encapsulation. This structural adaptability allows dendrimers to overcome biological barriers, enhance solubility, and achieve targeted delivery with reduced systemic toxicity.

In drug delivery, dendrimers can be engineered to carry therapeutic agents directly to diseased cells, improving bioavailability and minimizing side effects. In diagnostics, their ability to conjugate with imaging agents and biomarkers facilitates early detection and real-time monitoring of disease progression. For gene therapy, dendrimers offer a non-viral alternative for nucleic acid delivery, with promising results in transfection efficiency and cellular uptake. In tissue engineering, their biocompatibility and tunable surface chemistry support scaffold development and regenerative applications.

With continued innovation in dendrimer synthesis, functionalization, and clinical translation, these nanostructures hold the potential to revolutionize therapeutic strategies. As research advances, dendrimers may unlock new paradigms in personalized medicine, enabling treatments that are not only more effective but also tailored to individual patient profiles. Ultimately, their integration into mainstream biomedical practice could significantly improve patient outcomes across a wide spectrum of diseases, from cancer and neurodegenerative disorders to infectious diseases and genetic conditions.

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