European Journal of Medicinal Chemistry 221 (2021) 113572

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Amine-terminated dendritic polymers as promising nanoplatform for diagnostic and therapeutic agents' modification: A review

Mahsa Delyanee [a], Somaye Akbari [b, *], Atefeh Solouk [a]

[a] Biomedical Engineering Department, Amirkabir University of Technology, Tehran, Iran
[b] Textile Engineering Department, Amirkabir University of Technology, Tehran, Iran

ARTICLE INFO

Article history:
Received 10 March 2021
Received in revised form
24 April 2021
Accepted 7 May 2021
Available online 25 May 2021

Keywords:
Diagnostic and therapeutic agents
Amine-terminated dendritic polymers (ATDPs)
Modification
Polyamidoamine (PAMAM)
Polypropyleneimine (PPI)
Polyethyleneimine (PEI)
Biomedical applications

ABSTRACT

It is often challenging to design diagnostic and therapeutic agents that fulfill all functional requirements. So, bulk and surface modifications as a common approach for biomedical applications have been suggested. There have been considerable research interests in using nanomaterials to the prementioned methods. Among all nanomaterials, dendritic materials with three-dimensional structures, host-guest properties, and nano-polymeric dimensions have received considerable attention. Amine-terminated dendritic structures including, polyamidoamine (PAMAM), polypropyleneimine (PPI), and polyethyleneimine (PEI), have been enormously utilized in bio-modification. This review briefly described the structure of these three common dendritic polymers and their use to modify diagnostic and therapeutic agents in six major applications, including drug delivery, gene delivery, biosensor, bioimaging, tissue engineering, and antimicrobial activity. The current review covers amine-terminated dendritic polymers toxicity challenging and improvement strategies as well.

Contents

* Corresponding author.
E-mail address: akbari_s@aut.ac.ir (S. Akbari).

https://doi.org/10.1016/j.ejmech.2021.113572
0223-5234/

1. Introduction

The bulk and surface structures of biomaterials as diagnostic and therapeutic agents, affect their biological response. The bulk of a biomaterial indicates the physicochemical properties that should have been considered during designing and manufacturing of them. Biomaterial source, molecular composition, porosity, and crosslinking strategies for the modulation of diagnostic and therapeutic agents characteristics are significant bulk parameters affecting cellular biological responses [1]. In biology and medicine, the surface properties of biomaterials play an essential role due to the critical reactions that take place on the interface between the biomaterials and tissues fluids. The reactions are determined by surface properties, for instance physiochemical, topographical, mechanical, biocompatible, and bio-functional characteristics. These reactions are essential to the ultimate success or failure of biomaterials. They begin with water adsorption, then biomolecule such as proteins adsorption, and later cell adhesion to the biomaterial surface [2]. The above-mentioned surface features strongly influence cellular behaviors (such as adhesion, morphology, alignment, and contact guidance). There has been considerable progress in understanding the relationship between cells and extracellular matrixes used to create mimetic biomaterials used in biomedical engineering. Some of the influencing factors are summarized as chemical structure, hydrophilicity, hydrophobicity, surface roughness, and surface morphology [3].

Most biomaterials may have excellent engineering properties but may not have a good interface with the biological environment. Modification, therefore, plays a crucial role since identified unique properties such as cytocompatibility and antimicrobial activity can be enhanced while attributing mechanical strength, robustness, and inertness to the relevant bulk materials [4]. Biomaterial modification also appears to be a more cost-effective and effective way to modify emerging traditional biomaterials to suit modern and ever-changing clinical needs. Changing the biomaterial characteristics represents a promising route to engineering biofunctionality at the material tissue interface to modulate biological responses. Nanotechnology approaches for the treatment were developed to circumvent several drawbacks in the modification methods. The area of using nanoparticles (NP[1]s) to modify the surface and the bulk of biomaterials has been of considerable research interest. Different types of nanoparticles have been studied extensively for this application, such as metals (silver (Ag[2]), gold (Au[3]), …), minerals (carbon nanotube (CNT[4]), halloysite nanotube, hydroxyapatite, silica, …) and polymeric particles (chitosan, alginate, polylactic acid, polylactic-co-glycolic acid, dendrimers, …) [5–7]. Dendrimers are defined as a family of synthetic polymers with unique structural features, three-dimensional architectures that are highly branched and well-defined. It illustrates the advantages of dendritic materials for property modification and their potential applications in diverse areas [8]. The current review focuses on amine-terminated dendritic polymers (ATDPs[5]) and their application in the bulk in addition to surface modification of biomaterials as diagnostic and therapeutic agents.

2. Dendritic polymers

Dendrimer's name comes from the Greek word δένδρον "Dendron" and "Meros", which means tree-like [9]. Based on their architecture, dendritic polymers can be divided into four different groups, random hyperbranched polymers, dendrigraphts, dendrons, and dendrimers as shown in Fig. 1 [10].

In the early 1980s, researchers from DuPont, Kim, and Webster coined the term "hyperbranched polymers" or HB[6] to define dendritic polymers as unsymmetrical branching [11]. They are highly branched and have three-dimensional structures, observed in Fig. 1A HBs were produced by one-step polyaddition, polycondensation, and radical polymerization. In various biomedical applications, hyperbranched polymers play an essential role. The main areas are gene, drug and protein delivery, biodegradable materials, modification of the surface and the bulk of materials, bioimaging agent, and bio interaction applications due to the lower price compared to dendrimer [12].

Dendrons and dendrimers are the subgroups of dendritic polymers most intensively investigated as shown in Fig. 1B. The structure of the PAMAM dendrimer consists of three parts as shown in Fig. 2: a core with two or more reactive groups; interior layers consisting of repeated branching units covalently attached to the core (each layer is called one "generation" (G[7])); and outer surface terminal functional groups [13]. It is possible to construct dendrimers with almost precisely defined architectures and compositions by managing specifics of the core, interior, and surface.

Most dendrimers are synthesized following either a convergent or a divergent route. Dendrimers are assembled from the core to the surface (inside out) using the divergent method. In a series of repeated reactions, active groups bind to monomers, forming new generations, and these coupling reactions increase with an increasing generation. While, in the convergent strategy dendrimers are produced from the outside to the inside. The synthesis starts with the creation of dendritic monomers, and then dendrimers are formed by the interaction between the monomers and a single reactive core. Other synthesis methods have been developed to decorate dendrimers with different surface functional groups, such as hyperbranching strategies, double-stage convergent strategy, double exponential dendrimer growth, and combburst, whereas divergent and convergent approaches are time-consuming and tedious [14].

In Fig. 1C, the dendrigraft or hybrid dendrimer as the other class of dendritic polymers is illustrated. It was introduced as Combburst® and as arborescent polymers in 1991 [15,16]. Typically,

[1] Nanoparticle.
[2] Silver.
[3] Gold.
[4] Carbon nanotubes.
[5] Amine-terminated dendritic polymers.
[6] Hyperbranched.
[7] Generation.

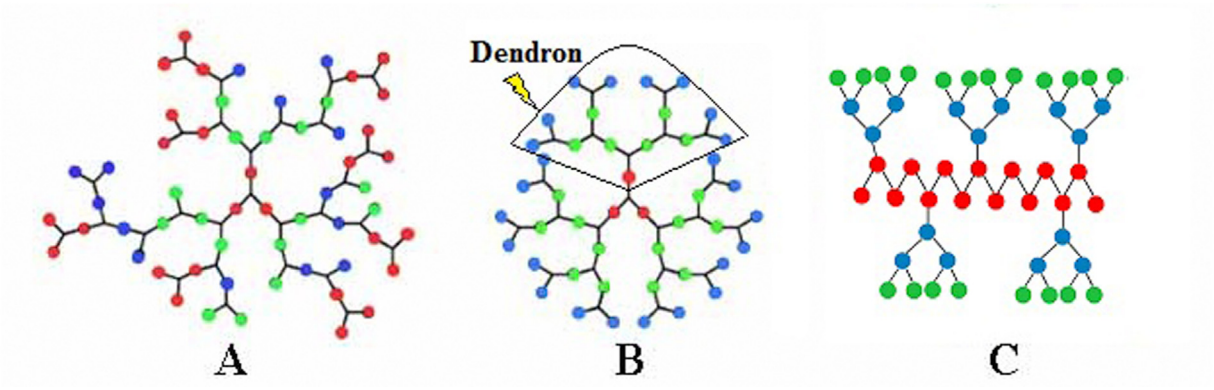

Fig. 1. Comparison of the structure of A). Hyperbranched, B). Dendrimer and C). Dendrigraft.

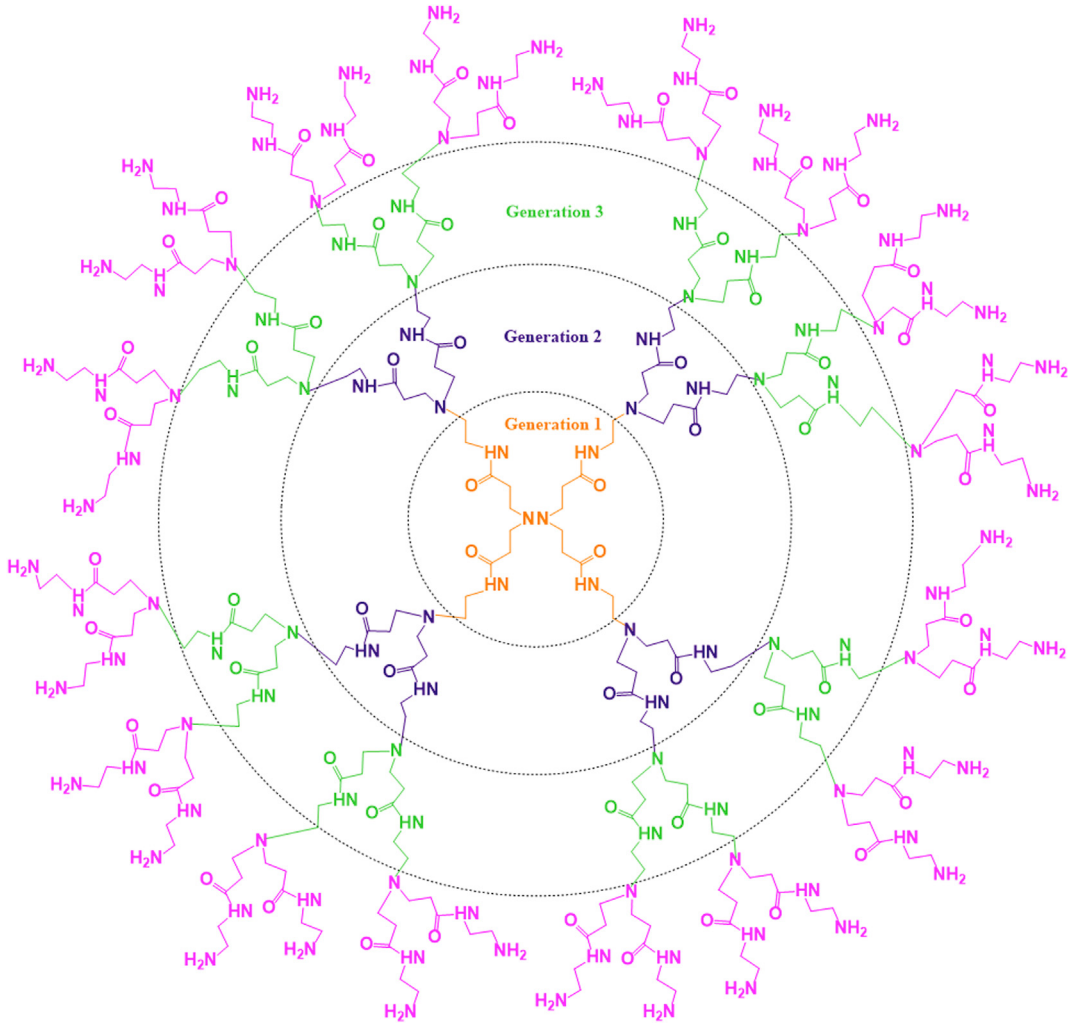

Fig. 2. Schematic reorientation of PAMAM G4 dendrimer structure.

dendrigraft polymers were produced by two methods including ionic polymerization and grafting. Three different strategies synthesized the dendrigrafts; the "grafting on" and "grafting from" methods, which are divergent techniques similar to the core-first dendrimer synthesis and the "grafting through" method, which is a convergent approach resembling the hyperbranched polymer [15–17].

Dendritic polymers are suitable for a variety of biomedical applications such as pharmaceutical applications (as drug delivery and target drug delivery systems, biomimetic artificial proteins,

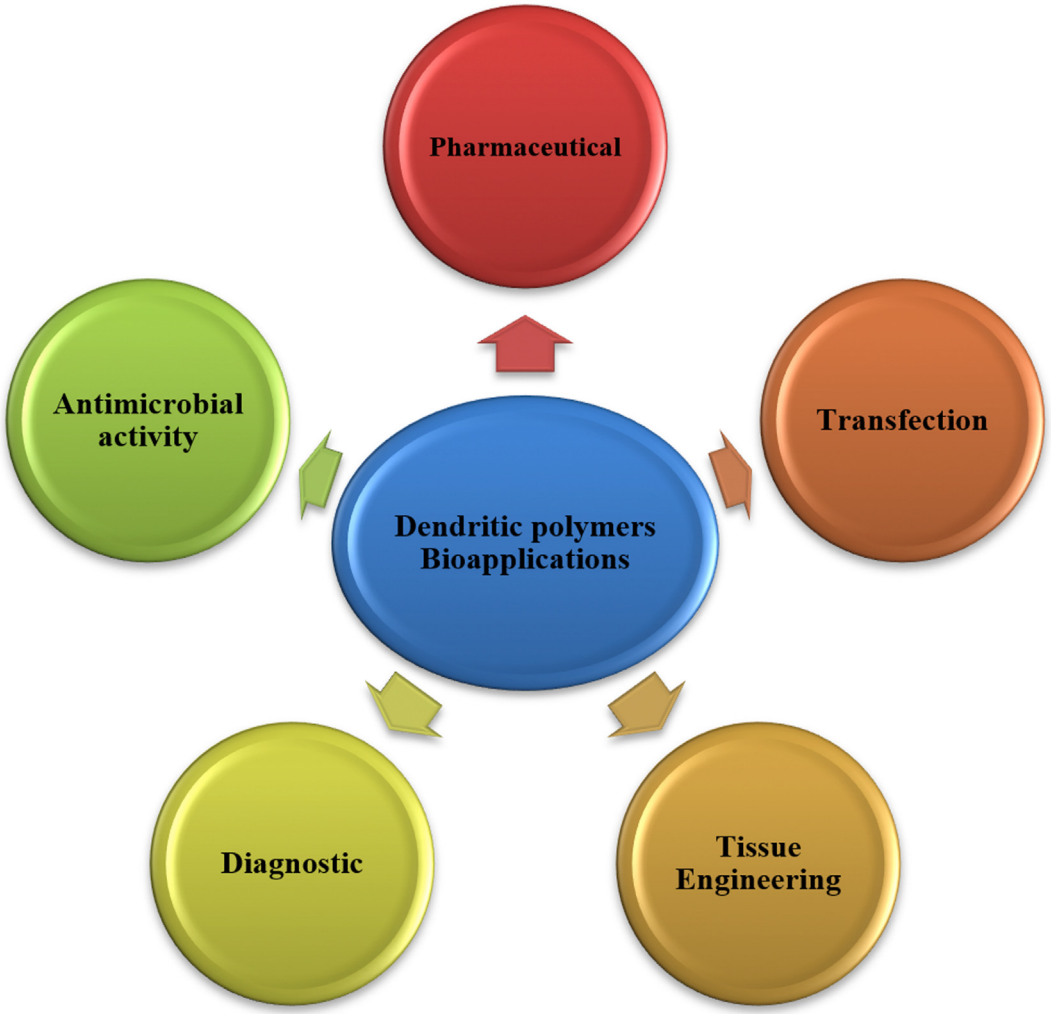

Fig. 3. Biomedical applications of dendritic polymers.

nanodrugs, and antibacterial agents), tissue engineering, transfection, diagnostic application (as molecular probes, X-ray and magnetic resonance imaging (MRI[8]) contrast agents), and antimicrobial agents [8,9,18–22]. This assortment can be seen in Fig. 3. Among various types of dendritic polymers such as poly(benzyl ether) dendrons marked as Frechet-type dendrimer, phosphorus dendrons, polylysine dendrimer, and poly(alkyl ether), ATDPs absorb remarkable attention which considered in this review paper.

3. Amine-terminated dendritic polymers

Amine-terminated polymers have been used as promising nanomaterials in biomedical engineering among various kinds of dendritic polymers [23,24]. For this reason, briefly, polyamidoamine (PAMAM[9]), polypropyleneimine (PPI[10]), and polyethyleneimine (PEI[11]) are described in the biomedical field as ATDPs.

PAMAM dendrimers are the first of the most widely studied ATDPs for biomedical applications such as drug and gene delivery, diagnosis, bioimaging, antibacterial agents, and nanoparticular synthesis [25–32]. They can be synthesized through divergent strategies. PAMAM has attracted significant attention because of its spherical shape, the high degree of monodispersity, flexibility, and controlled molecular architecture. This core-shell structure of PAMAM grows in linear diameter as a function of added generations, while at each generation the surface groups exponentially amplify. The diameters of these spheroids are systematically increasing at a rate of around 1 nm per generation. The sizes and contours of many essential proteins and bioassemblies match closely to them. For example, generations 3, 4, and 5 of the ammonia-core PAMAM dendrimers are approximately the same size and shape as insulin (3 nm), cytochrome C (4 nm), and hemoglobin (5.5 nm) [8]. Through molecular dynamic simulations, Goddard et al. [33] demonstrated that the presence of solvent in PAMAM dendrimers results in considerable size alterations. In other work by Luo and Imae [34], it has been shown that PAMAM dendrimers aggregate in aqueous solutions, resulting in changes in their normal size. In 2009 the size distribution was reported to have changed as a function of the time. The aggregate size increased over time and achieved a stable value [35]. The small size of PAMAM allows them to quickly cleanse through the kidneys from the blood and eliminate the need for biodegradability. Depending on the generation of PAMAM, different functional groups exist on the

[8] Magnetic resonance imaging.
[9] Polyamidoamine.
[10] Polypropyleneimine.
[11] Polyethyleneimine.

surface of the dendrimer (e.g., cationic G4-NH_2 and anionic G3.5-COOH), providing different functional groups and surface load on the PAMAM, enabling well-modified functional molecules [36]. As the PAMAM generation grows, the density of the surface functional groups increases. This can provide more reactive spots for attaching drugs, enzymes, antibodies, and nucleic acids to molecules. PAMAM dendrimers interact with nucleic acids due to functional amine groups, via electrostatic interactions. An important and influential factor in the complex's cellular uptake, created by the electrostatic interaction between cationic dendrimers and anionic DNA/RNA, is its size. Meaning the smaller the complex is, the better it penetrates [9]. Effective transfection for PAMAM has been shown to be typically restricted to more than G4 [37]. There are some issues in MRI application, including low contrast efficiency, no tissue specificity, and rapid excretion. Researchers have considered the use of dendritic structures such as PAMAM to prevent large amounts of agents from reducing the mentioned limitations [9].

Polypropyleneimine dendrimers, with the different biomedical applications, represent one of the most explored classes of dendrimers. Though different methods synthesize PPI dendrimers, this type of ATDPs is synthesized by a generally divergent method. Lower generations have an open and asymmetric shape with fewer interior spaces, encapsulating the guest molecule, and showing a high polarity range. So, they interact easily with protein-like myoglobin compared to older generations [23]. The idea that modified PPI dendrimers can cross blood brain barriers, a highly selective permeable membrane border that separates circulating blood from the brain has attracted research into applying this material in the delivery of drugs and genes [38,39]. PPI dendrimers improve the transfection of DNA by endocytosis and eventually through the cell nucleus as non-viral gene transfer agents. The complex stability of the PPI dendrimer-DNA/RNA and the net cationic charge increase with increased dendrimer generation [40]. Also, PPI dendrimers provide a platform for anionic DNAs and RNAs to be delivered efficiently because they contain internal tertiary and peripheral primary amines, allowing for easy surface modifications. However, there is a difference in polarity and size of the PPI and PAMAM dendrimers in their interior branched regions [41]. There are only alkyl and tertiary amine groups in the internal structure of PPI dendrimers. Whereas PAMAM dendrimers also contain amide groups, which enhance the polarity of their inside pockets [42]. Differences between internal functional groups often generate distinct host behaviors for guest molecules encapsulated [43].

The third amine-terminated structure introduced as PEI, a 1:2:1 ratio of aliphatic polymer, contains primary, secondary, and tertiary amino groups. As the polymer comprises recurring ethylamine groups, PEI is highly water-soluble and useable in linear and branched structures (the ranging of molecular weights 700−1000 kDa) [24]. PEI has also been identified as being reasonably safe for the internal utilization of animals and humans. PEI is widely used to flocculate cellular contaminants, nucleic acids, lipids, and cellular homogeneous debris to aid in purification soluble proteins [44]. Another field in which PEI has been used is enzymatic reactions in bioprocesses: as an immobilizing agent for biocatalysts [45], as a soluble enzyme carrier [46], or as a macrocyclic metal complex mimicking metalloenzymes [47]. Several studies reported using PEI in biomedical engineering, including a carrier for small drugs delivery, the photodynamic therapy, antimicrobial coating, the nanosized vectors preparation, and non-invasive optical bioimaging devices [24,48,49].

Although, amine-terminated materials are among the most promising polymers for biomedical applications, there are safety concerns regarding their toxicity. We will discuss their toxicity challenge after introducing the applications of PAMAM, PPI, and PEI for bulk and surface modification of biomaterials.

4. Biomedical applications of modified diagnostic and therapeutic agents with amine-terminated dendritic polymers

4.1. Drug delivery

Drug delivery systems (DDS[12]) can be designed to improve drug administered pharmacological and therapeutic properties [50]. The advantages of DDS include continuous maintenance of drug levels in patients, reduced amount of drug required, reduction of side effects due to targeted delivery to a particular site, and facilitation of short-lived drug administration (e.g., peptides and proteins). However, the following concerns should be considered in each DDS: (1) toxicity of the drug-carrying ingredients or products resulting from their degradation during release or sudden release (unwanted and rapid drug release); (2) the suffering felt from the drug delivery system itself or how it is injected; and (3) the system's expenditure on drug encapsulation or manufacturing materials [51,52].

Dendrimers have been of great interest as spherical branched macromolecules possessing many terminal groups and their use in drug delivery systems, DNA, and proteins [53]. In addition, the large number of functional surface amine groups on the surface of ATDPs can be altered or combined with different guest molecules [54]. The combination of specific targeting molecules such as sugar, folic acid, biotin, antibody, peptide, and dendrimer growth factors may result in preferential cargo distribution in the targeted tissue or cells [55]. However, there are still some difficulties in introducing dendrimer-based drug carriers, such as the limited scale of dendrimers, leading to rapid clearance of blood circulation [56−58]. In the DDS application, the main advantages of dendrimers are: reducing the required dose of a drug, increasing treatment efficacy, controlling drug biodistribution, decreasing drug side effects, increasing targeted drug delivery, easy detection with fluorescent samples, introducing multiple routes of administration, and having high drug-loading capacity [59−61].

In the field of biomaterial modification, several papers reported the use of ATDPs. Some of those publications that mentioned PAMAM, PPI, and PEI in drug delivery systems for performance enhancement and property improvement were summarized in Table 1.

4.1.1. PAMAM in drug delivery

PAMAM dendrimer provides an excellent DDS platform, characterized by a high degree of dendritic branches and high density functional amine groups. It has advantages such as high drug loading, high capacity for water bonding, and low toxicity. This section will introduce instances of using PAMAM to modify other drug delivery systems, regarding to these points.

Scientists have been exploring the capability of nanohybrids consisting of dendrimers and nanotubes for biomedical applications. Although both dendrimers and CNTs have shown great potential in drug delivery, due to toxicity and dispersibility issues, their promising clinical applications are still suspected. Hybrids of CNTs and dendrimers were reported to be able to remove the demerits of each other while synergizing the potential and potential toxicity of nanohybrids on which various reports distinguish in testing [62]. In another work to overcome the poor stability and bioavailability of berberine hydrochloride and chrysophanol as potential treatments for ocular diseases, a compound liposome system was prepared for PAMAM G3 as a carrier that can simultaneously clog these drugs. They reported the PAMAM G3-coated

[12] Drug delivery systems.

Table 1
Applications of modification with amine-terminated dendritic polymers for DDS.

Type of amine-terminated dendritic polymers	Generation or molecular weight	Type of drug delivery system	Drug	Comment	References
PAMAM	G1 and G3	MSN	DOX	The nanocarriers have self-fluorescent properties that prohibit the use of fluorescent labeling and allow pH-reacted drugs to be released.	[66]
	G4	Polystyrenesulfonate Microcapsules	DOX	Control loading and release of DOX and exploiting presence of dendrimer in the PAMAM G4 modified capsules to prepare crosslinked membrane films that were amenable to surface modification	[78]
	G3	Polyhydroxyalkanoate	Tamsulosin	The solubility of drugs is allegedly improved by dendrimers with a terminal amino group	[79]
	G2, G3, G4, andG7	Magnetic nanoparticles (Fe_3O_4)	DOX	Modified G4 dendrimer Fe3O4 releases most of the drug at lower pH, proving to be the most acceptable generation for the successful delivery of DOX	[65]
	G4	Chitosan nanoparticles	Methotrexate	Improve the cytotoxicity of free methotrex-ate on cells	[80]
	G3	Gelatin and cellulose nanocrystal	Betamethasone sodium phosphate	Rather loading efficiency and decrease the rate of degradation almost two times with high cell viability	[81]
	The reducible polyamidoamine	Iron oxide nanoparticles	DOX	The exciting promise of easy design in drug delivery applications have been demonstrated by cell and animal experiments.	[63]
PPI	G5	Au nanoparticles	DOX	Increased grafting ratio allowed the release of drugs due to the shielding effect of grafted dendrimers.	[71]
	G4	Au nanoparticles	DOX	Better solubility of drug in release media with respect to dendrimer cavities and drug release through polymeric matrix	[82]
	G4	Nanocrystalline cellulose	DOX	Higher amount of drug loading at different pH values	[70]
	G1-G5	MSN	Model drug	Dendrimers G1 and G2 have been shown to be more successful than higher generations in model drug preservation and eventual release.	[69]
	G5	Muramyl dipeptide	Amphotericin B	There was a significant reduction in toxicity in hemolytic toxicity and cytotoxicity studies in erythrocytes and J774A.1 macrophage cells.	[73]
PEI	1.8 kDa	Sialic acid -cholesterol	DOX	The highest tumor inhibition levels effectively impeded/delayed the disposition of the mononuclear phagocyte system	[77]
	1.8 kDa	Gelatin nanoparticles	Ovalbumin and polyinosinic: polycytidylic acid	Effectively adsorbed Ovalbumin/polyinosinic: Polycytidylic, facilitated cellular uptake	[75]

compound liposomes showed considerable cellular permeability in human corneal epithelial cells and increased bio-adhesion on corneal rabbit epithelium [62]. Novel chitosan derivatives with polyamidoamine moieties have been reported to be synthesized to encapsulate anticancer drug-methotrexate to enhance efficacy and reduce side effects. Results showed that chitosan derivatives with PAMAM could significantly improve the cytotoxicity of free methotrexate on cells and demonstrate that this new carrier can provide an appropriate platform for water-insoluble delivery of drugs [63]. Previously our group published a paper on polycaprolactone/PAMAM-G2 nanofiber was prepared to improve polycaprolactone deficiencies by direct aminolysis. It was to introduce active groups of NH_2 and OH into polymer surface and bulk polycaprolactone. The scaffold had intense cytotoxic activity by curcumin against breast cancer cells, incorporated in the nanofibers as an anticancer drug. High death rates for cells indicated that these scaffolds are highly effective as a novel drug carrier [64].

Functional groups, perfection in symmetry, nanosize and internal cavities makes a dendrimer-coated magnetic nanoparticle a suitable novel approach for DDS. They can also be targeted in a magnetic field towards the tumor site. Various generations (G2, G3, G4, and G7) of PAMAM were used to obtain modified magnetic nanoparticles (Fe_3O_4) to achieve an effective targeted delivery system for doxorubicin (DOX[13]). The results indicated that the low-generation characteristics of these nanoparticles had pH-sensitive drug release. G4 dendrimer-coated magnetic nanoparticles were the most suitable generation for efficient DOX delivery, which releases most of the drug at lower pH [65]. In 2015, the layer-by-layer assembly method was used to prepare multifunctional mesoporous silica nanoparticles (MSN[14]) with biocompatible PAMAM dendrimers and chondroitin sulfate, as shown in Fig. 4. It was investigated to overcome severe limitations encountered by using MSN and dendrimers alone and increased their performance in cancer treatment applications. Due to its incorporation in MSN, PAMAM dendrimers could avoid the rapid clearance, and chondroitin sulfate was used as binding points to bring together dendrimers. The results showed an increase in delivery performance through the targeted capability as DDS of modified nanoparticles [66].

4.1.2. PPI in drug delivery

Researchers have paid great attention to the use of PPI dendrimer as drug delivery systems [67,68]. In the following, examples of using this kind of dendritic polymers to modify other drug carrier structures will be introduced.

The effectiveness of PPI dendrimers modification on MSN in controlling the release of model drugs has also been studied [69]. PPI dendrimers G1 and G2 were more effective than higher generations in model drug retention and subsequent release. In other work, the nanocrystalline cellulose nanoparticles impregnated with PPI dendrimer were synthesized. They were combined with biocompatible folic acid, one of the most promising candidates with the potential for specific cancer cells targeting due to its high affinity to folate receptors. PPI modification was attributed to the more incredible amount of drug loading for nanocrystalline cellulose-G4 [70].

As we know, dendrimer-based hybrid materials have been

[13] Doxorubicin.

[14] Mesoporous silica nanoparticle.

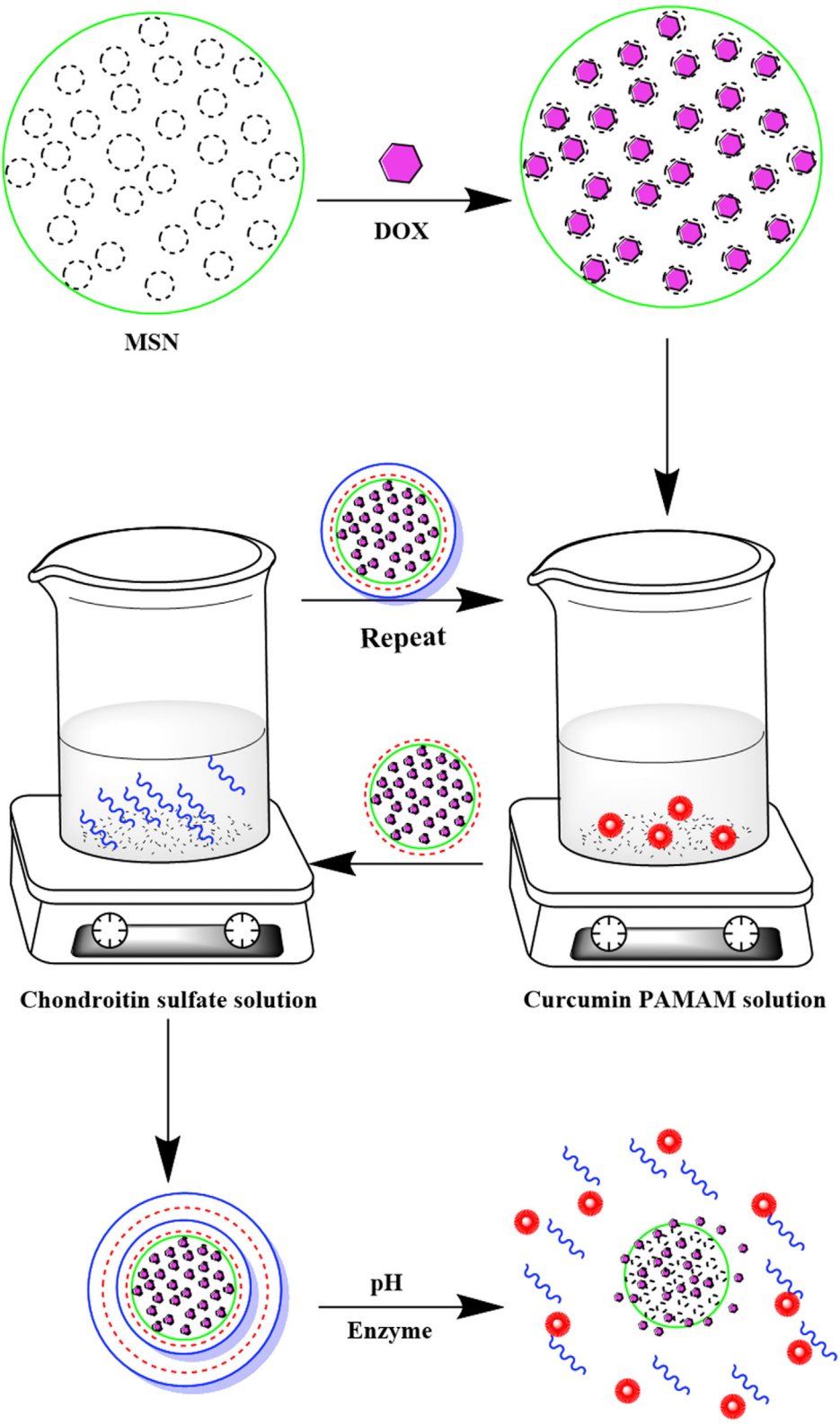

Fig. 4. Schematic representation of the preparation process of modified MSN.

extensively used in various applications, especially those reported in catalysts and sensors as dendrimer/Au hybrid nanoparticles. Najafi et al. [71] used various quantities of PPI to modify Au nanoparticles' surface through "grafting to" approach. The DOX drug was loaded onto the different synthesized hybrid nanoparticles, and under diverse circumstances, the release behavior was examined. The results revealed that carriers did not release the drug dramatically at pH = 7.4, while up to 92.8% of the drug release

was estimated at pH = 5.3. The higher grafting ratio also limited the release of the drug because of the shielding effect of the grafted dendrimers. Direct ligand exchange on citrate gold nanoparticle provided monodisperse Au NP-cored PPI dendrimers with a diameter of about 20 nm [72]. The ATDPs were found to be soluble under basic conditions up to pH 14. Au NP-PPI G3 also had exceptional stability: it was soluble in only one PBS buffer, can withstand high salt concentrations, and can be dried and redissolved without losing its properties. Because of its stability and ability to avoid lysosomal degradation, Au NP-PPI G3 was a promising drug delivery platform.

The use of muramyl dipeptide conjugated PPI G5 dendrimers to deliver amphotericin B to macrophages was defined in other study [73]. The therapeutic efficacy and toxicity of a dendrimeric muramyl dipeptide amphotericin B formulation were compared to marketed formulations. There was a significant reduction in toxicity in hemolytic toxicity and cytotoxicity studies in erythrocytes and J774A.1 macrophage cells.

4.1.3. PEI in drug delivery

The other amine-terminated dendritic polymer that was used for DDS modification is PEI. Nanoparticles based on gelatin are considered a promising carrier for both the antigen and the immunostimulant. It be delivered intranasally to induce an effective immune response [74]. Gelatin based nanoparticles were synthesized and modified with PEI as a carrier for an intranasal vaccine formulation consisting of negatively charged ovalbumin and polyinosinic: polycytidylic acid. The results showed that nasal administration of ovalbumin/polyinosinic: polycytidylic loaded gelatin nanoparticles elicited effective mucosal and systemic immune responses, which could be useful for further antigen applications delivery [75].

PEI escapes degradation in the lysosome's acidic environment by tending to bind negatively through the “proton sponge” process [48]. The “proton sponge” theory suggests that unprotonated amines in PEI absorb protons as they are injected into the lysosome, resulting in more protons being pumped in and an increase in Cl^- ions and water influx. The rupture of the lysosomal membrane and subsequent release of its contents into the cytoplasm is caused by a combination of osmotic swelling and swelling of the PEI due to repulsion between protonated amine groups [76].

In another work, PEI was selected to improve the therapeutic efficacy of chemotherapeutic. The other study in 2019 aimed to target tumor-associated macrophages and improve intracellular transport of DOX-loaded liposomes, synthesizing, and decorating the sialic acid-PEI-cholesterol conjugate on the drug-loaded liposomes [77]. It was supposed to be a safe and effective PEI complex preparation for clinical sarcoma treatment through the delivery strategy of targeting/deletion.

4.2. Gene delivery

As a transformative aspect in clinical medicine, gene therapies need to be overcome by the absence of safe and effective products to carry genes to target tissues [83]. There are disadvantages to using viral vectors such as adenoviruses, adeno-associated viruses, and retroviruses as gene delivery agents. It can get high levels of protein expression from these viral vectors. However, they endured from safety issues, immunogenicity, scale-up of development and the small size of the delivered genome [84]. Therefore, cationic polymers, liposomes, and dendrimers are synthetic delivery mechanisms that have been developed as a safer alternative to viral transfection [85]. Table 2 listed some examples of amine-terminated dendritic polymers that have been reported to modify systems of gene delivery.

4.2.1. PAMAM in gene delivery

To improve the deficiencies of gene delivery systems, PAMAM dendrimers that contain large numbers of primary amine and tertiary amine groups on the surface or interior emerge as promising non-viral vectors for the delivery of genes. PAMAM dendrimers are non-immunogenic and are efficient for other vector modification [86,87].

PAMAM modified carbon nanotube surfaces has proved to be the effective non-viral agents for gene transfer due to various functionalized multi-walled CNTs having already shown potential benefits for gene delivery. A comprehensive study was published of the various PAMAM dendron-functionalized CNTs in cellular absorption, cytotoxicity, and complexation of small interfering RNA (siRNA[15]). They reported lower toxicity of these hybrid nanocomposites in comparison to the individual carbon nanoparticles or dendrimers [88].

A challenge in loaded biodegradable microparticles preparation with plasmid DNA (pDNA[16]) applying the previous method (double emulsion solvent evaporation) was to damage pDNA, thereby denaturing or inactivating it due to manufacturing processes. Avoiding the exposure of pDNA to processes may be possible since plasmid DNA may be linked to the surface of cationic microparticles. PAMAM dendrimers are a promising class of cationic polymers which complex efficiently with pDNA. PolyD,L-lactide-co-glycolide microparticles charged with PAMAM-pDNA were prepared, characterized [89]. The *in vitro* investigations showed low toxicity, high pDNA loading and high transfection efficiencies that were not diminished in the presence of serum.

The other approach was to modify magnetic nanoparticles with various generations of PAMAM dendrimers and mixed with antisense survivin oligodeoxynucleotide. Pan et al. [90] reported that the composites of antisense oligodeoxynucleotide-dendrimer-magnetic nanoparticles were successfully synthesized and entered tumor cells within 15 min. The results indicated that composites of G5 antisense survivin oligodeoxynucleotide-dendrimer-magnetic nanoparticles exhibit the highest cellular transfection and inhibition efficiencies.

Another gene transfection system was reported in which PAMAMs G2 was covalently attached to the surface of a mesoporous nanosphere silica material, as shown in Fig. 5. PAMAM G2 capped MSN was used to complex with pDNA. The gene transfection effectiveness, cellular uptake, and biocompatibility of PAMAM G2-MSN with neural glia, human cervical cancer, and chinese hamster ovarian cells have been examined. Significant green fluorescent protein expression was observed [91].

4.2.2. 4-2-2 PPI in gene delivery

Among all of the dendritic polymers, PAMAM and PPI are the most-investigated ones in gene delivery [92]. The ATDPs have, in principle, the high positive charges density. Cationic polymers are believed to transfer genes through the mechanism of proton sponge. In 2016 the comparison of amine-terminated dendrimers to various linkers was investigated. The transfection efficiency of the conjugates of graphene oxide-polycation was evaluated. Although the viability amount of unmodified PAMAM and PPI was reported to be about 70%, in the case of PAMAM dendrimer-based carriers, it reached 90%. Cytotoxicity was even lower for PPI-

[18] Multi-walled carbon nanotube.

[15] Small interfering RNA.

[16] Plasmid DNA.

Table 2
Applications of modification with amine-terminated dendritic polymers for gene delivery.

Type of amine-terminated dendritic polymers	Generation or molecular weight	Hybridized with	DNA/RNA type	References
PAMAM	G4	Carbon nanohorns	siRNA	[88]
	G0,G1 and G2	Carbon Nanotube	siRNA	[102]
	G3-G6	PolyD,L-Lactide-co-Glycolide Microparticles	pDNA	[89]
	G1-G5	Multi-walled carbon nanotube (MWCNT[18])	Antisense c-myc oligonucleotides	[103]
	G4	MWCNT	pDNA	[104]
	G4	Graphene	pDNA	[105]
	G4	Polylysine	pDNA	[106]
	G2	Mesoporous silica nanosphere	pDNA	[91]
	G5	Selenium nanoparticles	siRNA and cisplatin	[86]
	G4	Single and multi-walled CNTs	pDNA	[107]
	G4	Polyethylene glycol-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine	siRNA drug co-delivery	[108]
	G4	Magnetic iron oxide NPs	siRNA	[109]
	G4 and G5	Polyethylene glycol-b-polypropyl methacrylate-co-methacrylic acid Poly-ethylene glycol-b-	siRNA	[110]
	G4	Polyethylene glycol-poly-L-lysine	siRNA	[111]
	G4	Hyaluronic acid	siRNA	[112]
PPI	G3	Graphene Oxide	pDNA	[93]
	G3	Cucurbituril	pDNA	[94]
	G2	Arginine	pDNA	[95]
	G2	Oligoethylenimine	pDNA	[96]
	G2	Poly(l-glutamic acid)	pDNA	[113]
PEI	25 KDa	MWCNT	pDNA	[114]
	25 kDa	Carbonyldiimidazole-activated polyethylene glycol	Antisense phosphorothioate oligonucleotides	[115]
	25 kDa	Superparamagnetic Iron Oxide Nanoparticles	pDNA	[98]
	(2 kDa and 25 kDa)	Polyethylene oxide	pDNA	[100]
	25 kDa	Methyl methacrylate	ShBMP-9 gene	[116]
	25 kDa	Hyaluronic acid	siRNA	[117]
	70 KDa	Polylactic-co-glycolic acid microparticles	pDNA	[101]
	PEI423, linear, M.W. = 423 and PEI1800, branched, M.W. = 1800	Iron oxide nanoparticles	pDNA	[118]
	25 kDa)	Au Nanoparticles	siRNA	[119]
	25 kDa	Magnetic-silk core-shell nanoparticles	Antisense oligodeoxynucleotides	[99]

conjugates, and viabilities were above 95%. Nanoplexes treated with PPI and PAMAM G3 were virtually non-toxic in all the transfection studies studied. Polycation-conjugated graphene oxide is expected to be used as a novel carrier in gene therapy because of its low cytotoxicity and high transfection efficacy [93]. Lim et al. [94] analyzed a ternary complex of PPI-1,4-diaminobutane dendrimer, DNA, and cucurbituril as a fully self-assembled gene delivery carrier. The complex was developed in a noncovalent manner, with DNA electrostatically interacting with PPI-1,4-diaminobutane and cucurbituril interacting with PPI-1,4-diaminobutane through several noncovalent interactions. According to the findings, the complex could transfect mammalian cells with high efficiency, with low cytotoxicity.

For plasmid DNA gene delivery systems, the arginine-conjugated PPI G2 was synthesized [95]. At a charge ratio of 150, the nanoplatform's size was measured to be about 200 nm. On HeLa and 293 cells, transfection efficiency was found to be 8–214 times higher than that of an unmodified messenger with 80–90% cell viability. Finally, arginine-conjugated PPI G2 had a 2–3 times higher transfection efficiency than PEI 25 kD, demonstrating its usefulness as a primary cell gene delivery carrier.

Oligoethylenimine-grafted PPI as degradable and biocompatible synthetic vectors for gene delivery was synthesized by Russ et al. [96]. Compared to their unmodified counterparts, grafted dendrimers were able to compact DNA to nanosized (100–200 nm) and showed improved colloidal stability. According to intravenous injection of grafted PPI, the tumor gene expression levels increased significantly with higher dendrimer core generation into tumor-bearing mice transgene expression.

4.2.3. PEI in gene delivery

PEI is one of the most efficient and cost-effective non-viral vectors, due to the ability of PEI, (e.g. Condensation DNA or RNA), and to protect them in harsh *in vivo* condition. PEIs with low molecular weight are promising to show decreased cytotoxicity. PEI (2 kDa) grafted with lipids was reported to have comparable transfection efficiency with low toxicity compared with 25 kDa [97]. A recent study used the method to linking PEI on magnetic nanoparticles to improve transfection performance through the use of a magnetic field. Examining the transfection efficiencies proved that the new generation actuation system developed could perform efficient transfection even within a short time (1 h) [98]. Another study with this approach was conducted by song et al. [99] to produce silk-PEI nanoparticles and magnetic-silk/PEI core-shell nanoparticles, using a simple one-step and cost-effective salting-out technique. The result showed that high uptake efficiencies (more than 70%) were achieved within 20 min through magnetofection.

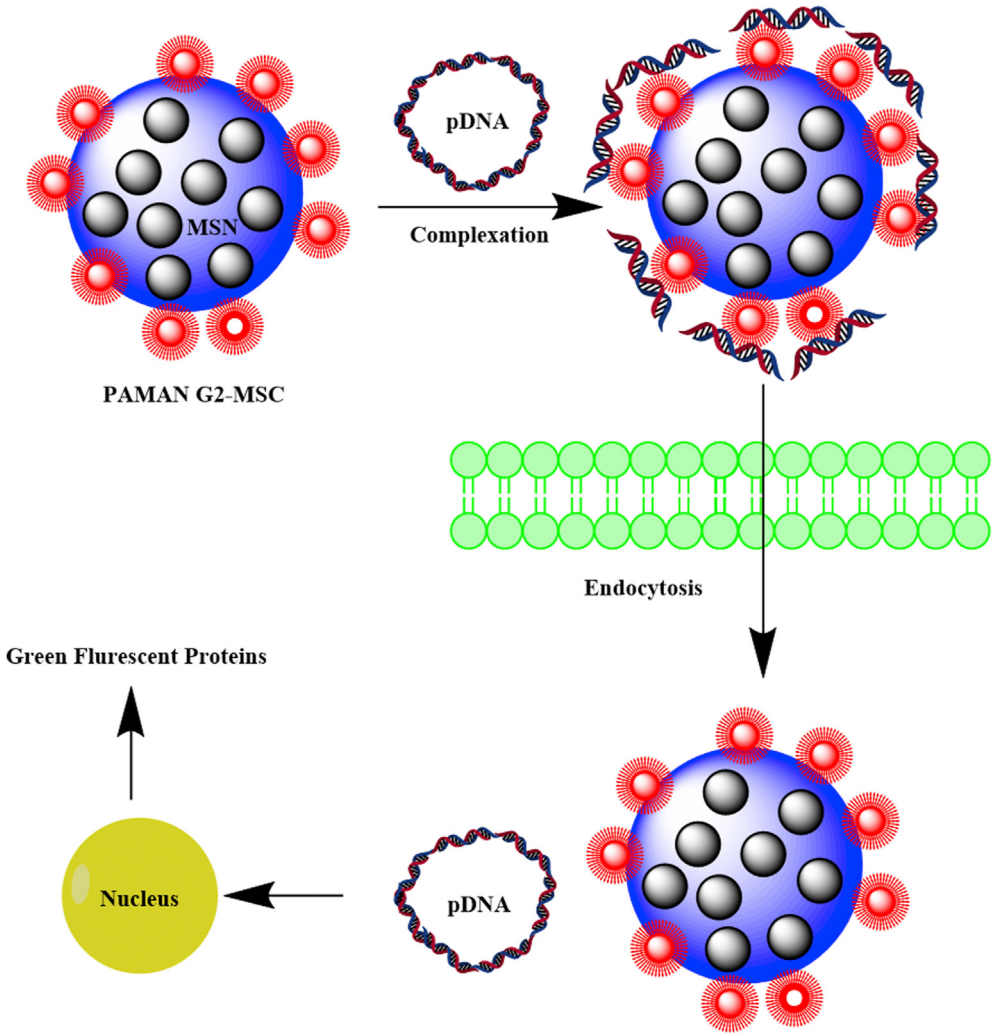

Fig. 5. Schematic representation of a gene transfection system based on a PAMAM G2 dendrimer-capped MSN material complexes.

The series of cationic copolymers were synthesized with non-ionic polyethers, polyethylene oxide (PEO[17]), or Pluronic 123 by grafting the PEI (2 kDa and 25 kDa). The particle size formed in this system varies from 70 to 200 nm, depending on the plasmid composition of the complex. All these conjugates are also stable over several days in aqueous dispersion [100]. The covalently surface-functionalized cationic polylactic-co-glycolic acid microparticles with PEI were created so that PEI conjugation yields non-toxic cationic microparticles with efficient pDNA charge. Results indicated that both DNA and protein were charged in the same particles, significantly improving the buffering capability of the particles and possible early phagosomal escape [101].

4.3. Biosensor

Dendrimers modifications of nanomaterials have several advantages for bio-sensing applications. In fact, some of these include having multiple conjugation sites, high-density functionalized, and stable structure of dendrimers. Some studies can be seen in Table 3 on the modification of amine-terminated dendritic polymers in the application of biosensors.

4.3.1. PAMAM in biosensor

PAMAM dendrimers have been confirmed as promising building blocks of molecular nanostructures. According to the literature, with a three-dimensional structure, PAMAM dendrimer has increased surface loading capacity and efficiency for the selective and sensitive detection of the molecule of interest [120].

The performance of the system in enzyme-based biosensors is extremely dependent on the enzyme stabilization and dissociation of the subunits [121]. A strong crosslinking between the dendrimer and the enzyme appears to be accomplished. This numerous covalent bonds between the enzyme and the dendrimer preserve the quaternary structure of the protein; the rigidity of the structures of the subunits is also increased. Biosensor technology is confronted by the synthesis of novel nanomaterials with enhanced electroconductive properties and the potential to recognize/immobilize analytical biomolecules.

In the construction of hybrid nanostructures, carbon-based nanomaterials have been useful for efficient use in biosensor preparation. Graphene hybrid derivatives have recently been considered for the construction of electrochemical biosensors, owing to the relatively low cost, large surface-to-volume ratio and remarkable electrical, mechanical, and thermal properties and biocompatibility of this nanomaterial. Fig. 6A is schematic preparation of a novel polyaminated graphene derivative. This bioelectrode displayed excellent electroanalytical activity with a rapid

[17] Polyethylene oxide.
[20] Glassy carbon.

Table 3
Applications of modification with amine-terminated dendritic polymers for biosensors.

Type of amine-terminated dendritic polymers	Generation or molecular weight	Type of sensing	Ligands	Electrode	References
PAMAM	G4	Alcohol Biosensing	Cysteamine/Alcohol Oxidase	Au Electrode	[136]
	G4	Catechol	Graphene oxide	Glassy carbon (GC[20]) electrodes	[122]
	G4	Glucose amperometric biosensor	Graphene oxide and platinum nanoparticles	GC electrodes	[123]
	G2	Carbon dots/Au nanocrystal	Carbon dots/Au nanocrystal	Glass carbon electrode as the working electrode, platinum wire as the counter electrode Ag/AgCl electrode as the referenceelectroe	[137]
		MicroRNA electrochemical biosensor	Multi-walled carbon nanotube and methylene blue redox indicator	GC electrode	[124]
	G4	Photoelectrochemical cell-sensor	Cds	Indium tin oxide	[138]
	G1	Electrochemiluminescence sensor	QDs and Au nanoparticles	Au electrode	[126]
	G4	Cathecol	Au nanoparticles	Au electrode	[139]
	G4	Glucose biomonitoring	Cysteamine	Au electrode	[140]
	G4	Aptasensor for the determination of thrombin	Cysteine	Au electrode	[129]
	G4	biosensing	Au nanoparticle network	Nanoporous anodic aluminum oxide	[141]
PPI	G2	Carcinoembryonic antigen	Carbon nanodots	Exfoliated graphite electrode	[130]
	G3	Extended-gate field effect transistor pH sensors	Nickel tetrasulfonated phthalocyanine	Quartz, glass, indium tin oxide, or Au covered glass substrates	[142]
	G2	Urea biosensor	Zirconia	Screen printed carbon elec-trode	[131]
	G4	Ultrasensitive detection of α-fetoprotein	Carbon nanodots	Modified GC electrode	[143]
PEI	25 kDa	Hydrogen peroxide in human serum	Au nanoparticle-copper protoporphyrin	GC electrode	[132]
	25 kDa	Cysteine	AuNPs- Anthraquinone-2-carboxylic acid	GC electrode	[133]

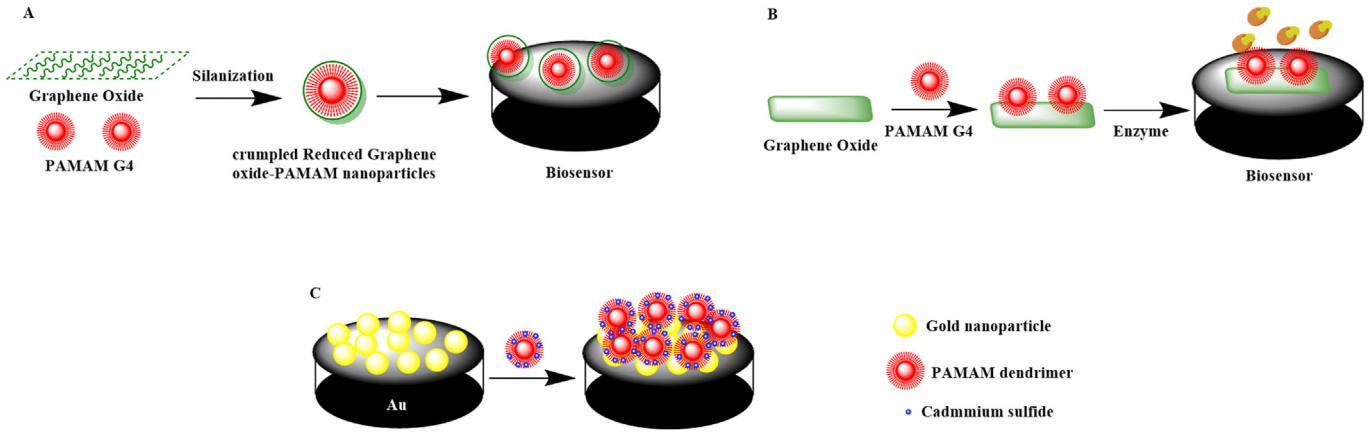

Fig. 6. Some schematic images of biosensors made with the presence of PAMAM dendrimers A). Preparation of a novel polyaminated graphene derivative, B). Preparation of hybrid nanomaterial and the further immobilization of the enzyme to build the nanostructured biosensor, and C). Synthesis of PAMAM-QDs assembled on the surface of the film Au Nanoparticles.

response of approximately 6 s and a low detection limit of 6 nM for catechol [122]. For a mediator with less glucose amperometric biosensor, graphene oxide crosslinking with polyamidoamine G4 dendrimer was used in other work as a decoration of platinum nanoparticles. The various steps involved in preparing of the hybrid nanomaterial and the further immobilization of the enzyme to build the nanostructured biosensor are shown schematically in Fig. 6B. The results showed that the biosensor exhibited strong electrocatalytic behavior for the oxidation of the enzyme-catalyzed reaction formed by H_2O_2, detecting glucose at +400 mV when poised [123]. As a simple and ultrasensitive microRNA electrochemical biosensor, a multi-walled CNT-PAMAM dendrimer and methylene blue redox indicator were reported in 2015. The proposed multi-walled CNT-PAMAM-based biosensor has excellent analytical properties for miRNA detection (high sensitivity, low detection limit, good selectivity, reproducibility, and regeneration properties) [124].

It was reported the advantages of synthesis semiconductor as a quantum dots (QD[19]s)-PAMAM composites lie in the preparation conditions. The various reactive groups on the dendrimer surface can make the composites significantly soluble in any solvent and

[19] Quantum dot.

can be applied to direct binding surfaces [125]. The nanocomposite film electrode preparation consisted of Au nanoparticles, which were first deposited directly on the electrode surface. Fig. 6C shows the synthesis of PAMAM-QDs assembled on the surface of the film Au Nanoparticles. The results indicated that the nanocomposite film electrode showed improved electrochemiluminescence response and excellent stability [126].

A DNA biosensor was developed using a modified electrode with PAMAM dendrimer and this sensor had functional DNA assembly capacity with favorable sensitivity and stability [127,128]. PAMAM's covalent immobilization on the electrode surface enhanced the immobilizing capacity of the probe molecules and magnified the response signal. The aptasensor exhibited favorable capacity, selectivity and stability for regeneration [129].

4.3.2. PPI in biosensor

PPI is one of the notable and fascinating dendrimers used as a platform for the manufacture of DNA, immune, and enzyme sensors in biosensors. The concept of a synergic combination of PPI and carbon nanodots has been reported to construct an immunosensor for the quantification of carcinoembryonic antigens [130]. The immunosensor exhibited excellent stability and was also selective in certain intervention species, such as ascorbic acid, glucose, alpha-fetoprotein, prostate-specific antigen, and human immunoglobulin [130]. Electrochemical biosensor based on electro-co-deposited zirconia-PPI dendrimer modified screen-printed carbon electrode urea. The biosensor has an amperometric response time ranging from 0.01 mM to 2.99 mM with 0.9985 correlation coefficient and 3.89 A $mM^{-1}cm^{-2}$ sensitivity [131].

4.3.3. PEI in biosensor

Another good co-reactant that can increase the electrochemiluminescence signal is polyethyleneimine, with many amino functional groups in its structure. The PEI-Au NPs were synthesized with PEI as a reducing agent and stabilizer by simple method and mild condition [132]. In the presence of dopamine, ascorbic acid, uric acid, and glucose, this sensor demonstrated outstanding selectivity, which had a satisfactory analytical efficiency for the identification of H_2O_2 in human serum samples, suggesting a successful application of biological sample processing [132]. A novel electrochemical cysteine sensor was synthesized by PEI-AuNPs-anthraquinone-2-carboxylic acid nanocomposite. The results showed that it was used to detect cysteine with recovering in the range of 95.78%–104.60% [133]. In another previous study, a novel solid-state $Ru(bpy)_3^{2+}$ electrochemiluminescence sandwiched immunosensor was built based on PEI-functionalized reduced graphene oxide for sensitive detection of α-fetoprotein, and AuNPs decorated polyamidoamine dendrimers [134].

Because the polycaprolactone structure lacked a functional group, PEI was blended with polycaprolactone polymer to provide functional amino groups on the nanofiber mat surface. One microorganism was first immobilized by covalent modification on the electrospun nanofiber mat. As a model analyte, polycaprolactone-PEI/G.oxydans whole-cell biosensor can therefore, be used to measure glucose [135].

4.4. Bioimaging

Bioimaging refers to techniques that picture biological processes in real-time. Yet digital technology is a comparatively new advancement in the medical field. Safety is the main challenge in this field; in other words, scientists try to use non-invasive ways for this aim. The dendritic structure, especially amine-terminated ones, is an ideal platform for covalently ligand targeting in multifunctional imaging due to its unique characteristics. This means that it could be possible to change different drawbacks excited in this area by integrating the surface functionality of the dendrimers and special molecular recognition ability with the properties of bioimaging agents.

The four most important commonly recognized nanotechnology platforms are known as QDs, nanotubes, fullerenes, and dendrimers, which create relatively specific nanostructures [144]. For bioimaging applications, the combination of the luminescent properties of thiol-capped QDs with 1–10 nm size was used as small semiconductor nanocrystals for biological labeling detection by PAMAM dendrimers with high carrier power. The findings revealed that the PAMAM-modified complex used for labeling gastric cancer cells was efficient and selective in its functioning [145]. In other study, QDs were modified with PAMAM dendrimer to increase cellular uptake and endosomal escape in supramolecular complex isolated from mice bone marrow. Results showed that by the PAMAM dendrimer modifying the uptake efficiency and cytosolic distribution of QDs in primary cultured mesenchymal stem cells [146].

As nano-biomaterials, carbon nanotubes have unique characteristics such as high aspect ratio, high surface area, high mechanical strength, ultralight weight, etc. These commonly used nanomaterials have particular electronic properties and exceptional chemical and thermal stability. These features make them a viable nanoplatform for biomedical applications to enhance the CNT's aqueous solubility by functionalizing the nanotube surface with polymers or small molecules. Fig. 7 schematically shows that the multi-walled carbon nanotubes (MWCNT[21]s) were directly functionalized with PAMAM G5 dendrimers, which were covalently linked to isothiocyanate fluorescein and folic acid. On the surface of multi-walled CNTs modified with strong acids, carboxyl residues allow the conjugation of PAMAM dendrimers with amine groups by chemical coupling. The findings revealed that both targeting ligands and imaging molecules could be altered CNTs by a single step dendrimer-mediated reaction. These multifunctional nanodevices were biocompatible, stable, and water dispersible [147].

Liu et al. [148] reported the size-controlled synthesis of PAMAM G5 dendrimer-stabilized silver nanoparticles for computed tomography (CT[22]) imaging applications. At the same molar concentration of the active element, X-ray absorption coefficient measurements show that modified nanoparticles' attenuation is size-dependent. The PAMAM G5 dendrimer-stabilized silver nanoparticles with a diameter of 16.1 nm have X-ray attenuation strength similar to that of a clinically used iodine-based contrast agent. Furthermore, CT scanning revealed long-term enhancement at the injection site of mice injected subcutaneously, indicating that they could be used as a CT contrast agent. Other research looked into the X-ray attenuation properties of dendrimer-entrapped gold nanoparticles that could be used as CT contrast agents [149]. PAMAM G5 modified Au NPs with a size range of 24 nm can be made by varying the molar ratio of gold salt to G5. NH2. The NPs produced are stable in water, PBS buffer, and cell culture media and at various temperatures (from 4 to 50 °C) and pH levels (pH 5–8). CT scanning of mice injected subcutaneously with those NPs showed substantial enhancement, and intravenous injection of them allowed X-ray CT imaging of mice.

In MRI, macromolecular contrasts agents were developed because they are retained longer in the vasculature than conventional small molecular contrast agents. PAMAM has been used as the central element of contrast agents. Researchers have conjugated PAMAM (G3-G6) to chelated gadolinium and assessed the

[21] Multi-walled carbon nanotubes.
[22] Computed tomography.

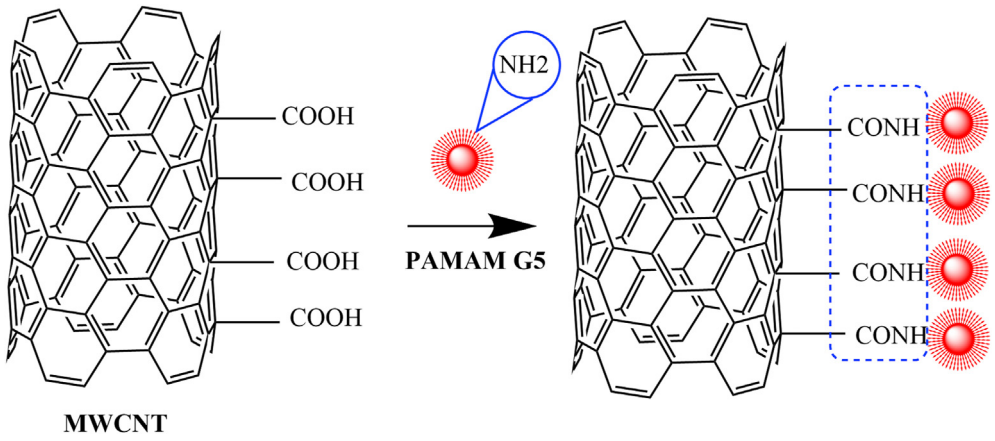

Fig. 7. Schematic representation of reactions to modify MWCNTs with PAMAM for cancer cell targeting.

relation between the size of these molecules and their pharmacokinetics. Results indicated that the contrast-enhanced MRI employing these agents offered very high quality and detail to fine vessels. Those contrast agents should also be useful for visualizing with tumors' neovasculature [150]. The inherent lack of MRI sensitivity requires the development of new contrast agents to extend this technique's application to cellular imaging. MRI contrast agents were produced by peptide coupling between an amidoamine dendron. Compared with monomers, an increase in longitudinal relaxivity was found for both structures. Results showed a substantial rise between 20 and 60 MHz [151].

For disease detection, therapy control, and prognosis assessment, positron emission tomography (PET) imaging provides physiological and biological information through PET agents' *in vivo* delivery [152]. In 2015, PAMAM G4 dendrimers were conjugated with tetraazacyclododecane tetraacetic acid mono (N-hydroxysuccinimide ester), and radiolabeling with Gallium-68 [153]. At pH 4, the dendrimer complex concentration of 11.69 mM given the highest radiolabeling efficiency of over 93.0%. The radiolabeled preparation was stable at room temperature and in serum for up to 4 h (radiolabeling efficiency of 96.0%). Animal PET imaging assisted the animal organ's biodistribution results, showing strong 'non-specific' tracer absorption in tumors and excretion mainly through the kidneys. PET and single photon emission computed tomography (SPECT[23]) have the highest sensitivity and are capable of quantitative visualization of functional details, which is critical for disease evaluation and diagnosis as well as personalized medicine. Nano-systems containing and integrating abundant imaging reporters, such as dendritic polymers, will dramatically boost the contrast signal for better imaging [154].

PAMAM G5 dendrimer was reacted with biotin and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetria minepentaacetic acid to produce the novel complex, which was then conjugated with avidin [155]. Following that, both conjugates were radiolabeled with technetium-99 m. The conjugate of dendrimer with avidin has a much higher cellular uptake in HeLa cells than biotin, according to their *in vitro* cellular uptake analysis. Both the *in vivo* biodistribution and micro-SPECT imaging studies indicated that the liver and spleen had high uptake, while the kidney had low uptake.

Carbon dots are the other biocompatible fluorescent nanoparticles considering their convenient synthesis, strong fluorescence, and high photostability. Polyethyleneimine has been used to modify carbon dots such as molecular and pH sensing, cellular imaging, gene, and vaccine delivery with bioimaging function. A novel synthetic strategy was reported for preparing multi-carbon dot crosslinked PEI particles, through self-assembly of hydrophobically modified PEI. The carbon dots/PEI particles have the photoluminescent carbon dot synergistic effect and crosslink-enhanced PEI emission. Resulting in superior optical properties such as high aqueous system fluorescence quantity yield (more than 66%), excitation-dependent emission effect, stable broad pH fluorescence, and resistance to photobleaching [156].

Nanoparticles of the magnetic iron oxide (Fe_3O_4 NPs) were used for magnetic resonance imaging. The Fe_3O_4 NPs are typically expected to be colloidally stable, have decreased reticuloendothelial system non-specific uptake, or have active targeting specificity making them effective for this application after functionalizing with targeting ligands. An effective strategy for the above requirements is a surface modification of the Fe_3O_4 NPs surface with hydrophilic and biocompatible polymers. Fig. 8 shows the surface functionalization of the PEI-modified iron oxide nanoparticles that have been reported for bioimaging. Prussian blue staining further confirmed the cellular iron uptake. It has been shown that the limited hemolytic activity of Fe_3O_4-PEI NPs with various surface modifications in a concentration lower than 400 μg/mL can make them a good candidate for biomedical application. The Fe_3O_4/PEI NPs had excellent water dispersibility with various surface functionalities and hemocompatibility were shown by colloidal stability. The results show that rich amine conjugation chemistry can be used for different biomedical applications, particularly MRI [157].

4.5. Tissue engineering

Tissue engineering is an interdisciplinary science that extends the concepts of engineering to the development of biological replacements that preserve, sustain, or strengthen the role of an organ as a whole. Consequently, the control of cell behavior on solid scaffold surfaces is essential for tissue engineering. Thus, the primary tissue engineering triad consists of cells, scaffolds, and bioactive agents that can be used in combination or independently. Many different materials were investigated as scaffolds, but in some cases, modifications are needed to improve performance [158]. A useful scaffold must fulfill different criteria and often contradictory ones. More advanced scaffolds can attempt to capture one or more cell types, organize them in spatially defined structures, and integrate various bioactive factors, (such as hormones, cytokines, or signaling molecules). The unique characteristic of dendritic polymers makes them promising candidates for various tissue engineering applications for instance crosslinking agents,

[23] Single photon emission computed tomography.

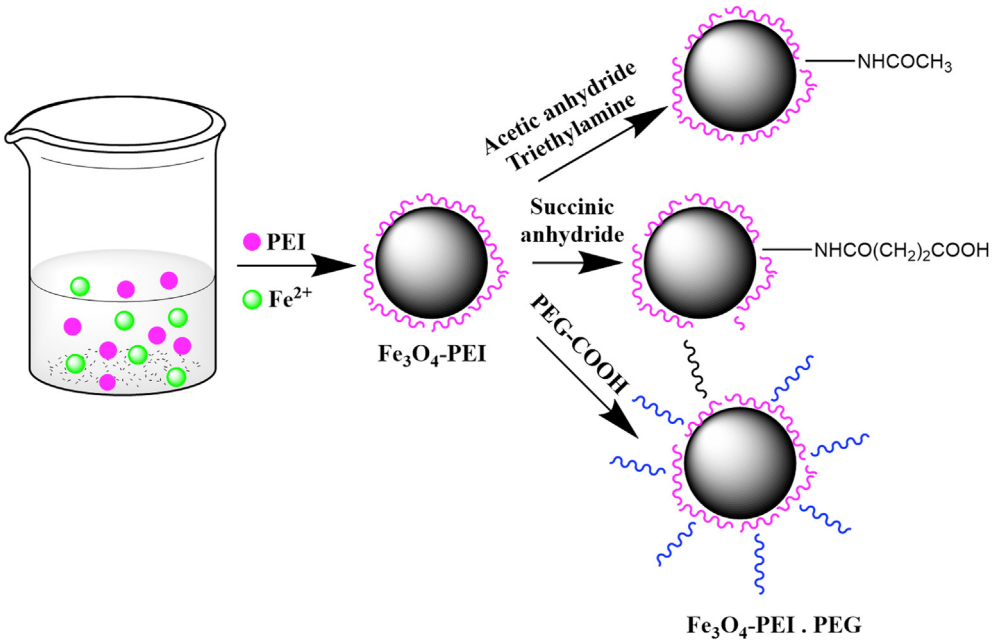

Fig. 8. Schematic illustration of the hydrothermal synthesis of Fe3O4–PEI NPs and the subsequent functionalization of the Fe3O4–PEI NPs.

surface charge modulators, and primary components in scaffolds structure to emulate extracellular matrices [25].

After activation of the substratum's functional groups, the multifunctional dendrimers were added as crosslinkers. Collagen scaffolds have been applied to tissue engineering such as cartilage, cornea, skin, etc. However, in its pure form, collagen is a weakly crosslinked thermo gel with mechanical properties that are not sufficient for most applications *in vitro* and *in vivo*, significantly restricting its ability as a biomaterial. There are some studies of using an ATDPs as crosslinker to collagen. Using PPI G1, G2, and G3 for this application, the findings suggest that the presence of a significant number of excess amine groups in the dendrimers can be effectively extended for collagen crosslinking without the need to use cytotoxic glutaraldehyde [159]. In other studies, the resulting mechanical properties of gels (based on collagen and PPI G2) were calculated for use as a corneal tissue engineering scaffold. The dendrimer crosslinked gels Young's module was substantially higher than that of the other crosslinkers, rising to 5 MPa compared to 0.1 MPa for the N-(3-dimethylaminopropyl)-N′-ethyl-carbodiimide crosslinked gels [160]. PPI was not only used as a crosslinking agent, but PAMAM was also used. The PAMAM crosslinked collagen scaffolds exhibited higher denature temperature and better tolerance to collagenase digestion relative to their counterparts without dendrimer. The human conjunctival fibroblasts proliferation revealed that the introduction of PAMAM improved the proliferation significantly [161]. In 2000, surface modification of polystyrene plates with PAMAM G1 was reported. The findings indicated that rat hepatoma cell lines adhered to an immobilized surface through contact between the dendrimer's terminal amino groups and the cell membranes. The adhered cells were stable, could proliferate, and displayed synthetic activity in the urea [162].

It was designed to analyze the mixture of the novel carboxymethylchitosan/PAMAM nanoparticles filled with dexamethasone. In the proliferation and osteogenic differentiation of rat bone marrow stromal cells *in vitro*, all scaffolds were used. Results showed that the nanoparticles improve osteogenesis by increasing alkaline phosphatase activity and mineralization of the extracellular matrix. The pre-incubation of stem cells with these forms of nanoparticles enables dexamethasone to be distributed inside the cells and directly affects their cellular fate, an exciting new method for cell and tissue engineering strategies [163].

Buckypapers were covered with a PAMAM in 2019, and their composition changed from hydrophobic to hydrophilic. By using the 3D printing technology, however, a custom system has been developed and produced that allows cells to expand on buckypapers for several days and studies their physicochemical properties for potential applications in tissue engineering [164].

Human bone marrow mesenchymal stromal cells are considered a potential cell source for mesenchymal stromal cells-based bone regeneration. Hong et al. [165] stated that PAMAM-modified polylactic-co-glycolic acid particles might serve as an intracellular estrogen delivery mechanism that effectively improves the capabilities of mesenchymal stromal cells and has good potential as regulator mesenchymal stromal cells to conduct the regulation of mesenchymal stromal cells effectively. The result suggested that it could increase the osteogenic capacities of mesenchymal stromal cells and establish suitable implantation environments for mesenchymal stromal cells-based bone tissue engineering [165].

A single-walled carbon nanotube (SWCNT[24]) graft copolymer was synthesized in 2005. Prepared by functionalizing single-walled CNTs with PEI, this polymer was used as a substratum for cultivated neurons and found to facilitate neurite outgrowth and branching. Fig. 9 illustrated a schematic of SWCNT graft copolymer (SWCNT-PEI) synthesis with branched PEI feature. The results of cell viability demonstrated the short-term survival and growth of neurons not only on the previously tested PEI substrates but also on the newly synthesized SWCNT-PEI graft copolymer. Such findings include a distinct vulnerability of growth cone forming, neurite outgrowth, and branching to the consistency of substrates, most likely surface charge [166].

In another study, two types of new CNT-nanohybrid materials were developed, MWCNTs PPI G2/hydroxyl apatite and MWCNTs-

[24] Single-walled carbon nanotube.

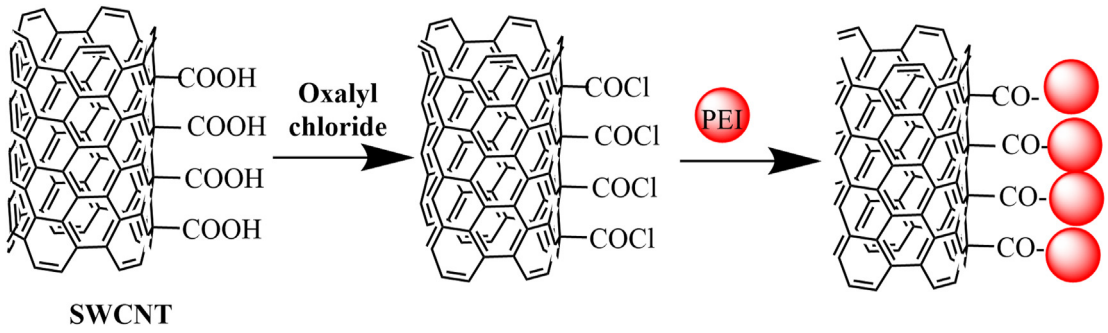

Fig. 9. Schematics of branched PEI functionalized SWCNT graft copolymer (SWCNT-PEI) synthesis.

PPI G3/hydroxyl apatite, to improve the application of anticancer activity and bone tissue engineering to mimic the bone extracellular matrix. The findings suggested that the newly produced MWCNTs-PPI(G3)/hydroxyl apatite nanohybrid could mimic all of the extracellular bone matrix qualities in terms of cell proliferation and was biocompatible, biodegradable and bioactive in normal human osteoblasts due to higher levels of hydroxyl apatite deposition [167].

Biodegradable aliphatic polyesters, such as polycaprolactone, polylactic acid, polyglycolic acid (FDA[25] approval biopolymers), and their copolymers have been considerably used in biomedical and pharmaceutical application. Polycaprolactone nanofibers are one of the most common types due to their distinct mechanical and chemical properties. Although the absence of a functional group on the surface of polymer is their disadvantage. Jing et al. [168] blended PEI into polycaprolactone nanofibrous vascular scaffolds by electrospinning methods. Their findings revealed that the fiber diameters and water contact angle decreased by raising the PEI content to 5% inside the scaffolds, while Young's modulus improved from 2.0 ± 0.2 to 4.1 ± 0.1 MPa. *In vitro* experiments have found that nanofibers containing 2% PEI have facilitated the attachment and proliferation of human umbilical vein endothelial cells.

In our previous study, nanofibrous scaffolds were modified by blending with PEI in various blend ratios, using polyL-lactic acid electrospun. Fig. 10 explains the electrospinning schematics process. From the analysis, the most promising findings were reported for the 85:15 blend ratios. It was chosen with gelatin for further modification. Our findings suggested that PEI could increase porosity, mechanical properties, hydrophilicity of the surface/bulk, and density of gelatin grafting about five times with positive impact on cell behaviors. It is to be noted that the disadvantages of polylactic acid electrospun nanofibers for potential use as a practical tissue engineering scaffold (i.e., poor cell adhesion and host tissue necrosis resulting from having acidic condition when degrading) may be resolved by mixing with PEI and greasing with gelatin [169]. Our research group has produced novel aminolyzed polylactic acid films and electrospun nanofibrous scaffolds with PPI-G2 and characterized them as possible substrates for tissue engineering. The results showed a considerable improvement in the hydrophilic properties of scaffolds. Biodegradation of polylactic acid has also been analyzed for 4 weeks using a pH value analysis. The declining pH values, which induced significant infusion and inflammation of immune cells in the medium by raising the acid rate due to secretion of the lactic acid, have been changed. The biological results show encouraging cell adhesion and viability stressed the beneficial properties of polylactic acid/PPIG2 scaffolds as a biodegradable biomaterial for biomedical implants [170].

[25] Food and drug administration.

4.6. Antimicrobial agents

The widespread use of conventional antibiotics has caused an increase in bacteria resistance, and raising the public health concern. That's why; research into new and efficient antimicrobial agents is desperately required. Dendrimers with unique structure and topological characteristics, such as high molecular uniformity, narrow molecular weight distribution, elastic scale, and surface charges, were investigated as antimicrobial agents [171]. The presence of hydrophobic branched in dendrimers allows their penetration into the bilayer of phospholipids leading to the bacterial membrane [172].

The antibacterial properties of ATDPs have demonstrated their potential to avoid biofilm formation and solve problems associated with conventional antimicrobials, including short-term antimicrobial residual toxicity and resistance growth in microorganisms [173–175]. Besides the antimicrobial effects of ATDPs, several studies use them to modify other materials such as antibiotic drug delivery, antibacterial nanoparticles, and functionalization of materials. Some studies in this application can be seen in Table 4.

Most studies mentioned in the previous parts consider ATDPs as modifier drug delivery systems. Also, the antibiotic agents were encapsulated within dendrimers or were covalently bound to their surfaces. The usage of dendrimers to increase the stability, solubility and release of pharmaceuticals into the blood were considered by drug carriers [178]. It has been reported that the effects of PAMAM G3 and G5 on vancomycin's antibacterial activity have been tested against two Gram-positive and four Gram-negative bacteria by assessing their minimum inhibitory concentration, minimum bactericidal concentration, and fractional inhibitory concentration index values. Results showed that vancomycin-PAMAM dendrimers displayed strong antibacterial effectiveness against Gram-negative bacteria resulting in a decrease in vancomycin values, and increased effect by G5 was greater than G3 by the decline of minimum inhibitory concentration values up to 64 times [189]. The difference in PAMAM G3 and G5 interactions with vancomycin was reported as the difference in their size, membrane interactions and entrapment efficiencies. More research is required to determine the actual mechanism of this effect. Antimicrobial activity of PPI G4 in the presence of ciprofloxacin was investigated against the reference strains of Gram-positive and Gram-negative. In both strains, the administration of PPI dendrimers and ciprofloxacin greatly enhanced its antibacterial impact relative to the cultures that obtained the drug alone. Ciprofloxacin and PPI dendrimers have been detrimental to bacterial strains at non-toxic concentrations for the eukaryotic cell [191].

Entirely generally researched are the antimicrobial effects of many elements, such as platinum, copper, gold, and silver [164]. Several studies indicate that Ag nanoparticles have good antimicrobial activity, especially against bacteria, which may lead one to

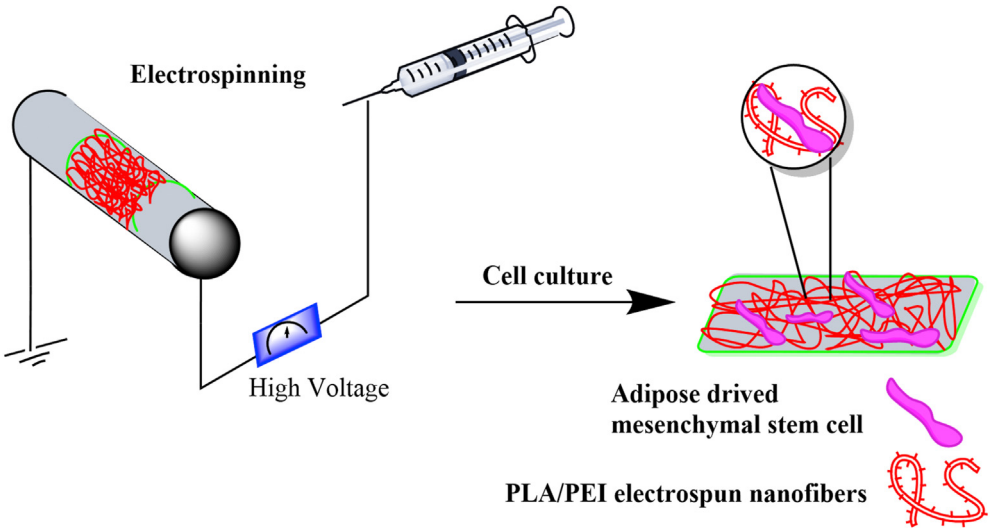

Fig. 10. Schematics of polyL-lactic acid/polyethyleneimine electrospinning and adipose-derived stem cells cultured on electrospun nanofibers.

Table 4
Applications of modification with amine-terminated dendritic polymers for antimicrobial agent.

Type of amine-terminated dendritic polymers	Generation or molecular weight	Modified materials or drug	Type of microorganism	Comment	References
PAMAM	G1-G3	Ag	E.coli	Exhibited the antibacterial effects	[176]
	G4	Ag	*S. aureus*, *P. aeruginosa*, and E.coli	High antimicrobial activity in several cases without the loss of solubility	[177]
	G4	Ag	*S. aureus*, Staphylococcus epidermidis, E.coli, and *P. aeruginosa*	Antibacterial properties against burn-wound infections	[178]
	G1-G3	Silica	*S. aureus* and *E. coli*	G3 dendrons was one of the most	[172]
	G4	Zinc Telluride	*S. aureus*, B. subtillis, *E. coli* and *V. cholerae*	Good antimicrobial activity against Grampositive bacteria	[179]
	G2	Chitosan	*S. aureus* and *E. coli*	Significantly improved antibacterial activity	[180]
	G3	Chitosan	*S. aureus* and *E. coli*	Significant antibacterial activity	[181]
	G2	Carboxy methyl chitosan	*S. aureus* and *E. coli*	Higher antibacterial activity against Gram-negative bacteria	[182]
	G5	Titanium Substrates	*P. aeruginosa* and *S. aureus*	Effectively inhibited the colonization of the gram negative bacteria	[183]
	G4	Hydroxyapatite	F.nucleaum,*S. aureus*, *E. coli* and S. sanguinis	Good antimicrobial activity	[184]
	G4	Erythromycin	*S. aureus* strain	Improved antibacterials activity	[185]
	G4	Quinolone	*E. coli*	Strong antimicrobial activities in the presence of dendrimers	[186]
	G2 and G3	Ketoconazole	Candida strains	More affecting antifungal activity	[187]
	G2 and G3	Erythromycin and tobramycin	*S. aureus*	Only slight influence on the antibacterial activity of EM	[188]
	G3 and G5	Vancomycin	*E. coli*, K. pneumonia, *S. typhimurium* and *P. aeruginosa*	Enhanced effect by G5 is more than G3	[189]
PPI	G3	Amoxicillin	*P. aeruginosa* and E.coli	Significantly enhance the antibacterial effect	[190]
	G4	Ciprofloxacin	*S. aureus* and *E. coli*	Shows the possibility of using it at lower dosages	[191]
	G4	Phage KP27 endolysin	*Pseudomonas aeruginosa*	Increasing an antibacterial effect	[171]
	G4	Nadifloxacin	E.coli, *P. aeruginosa* and P. hauseri	Dendrimers allows using lower doses of the antibiotic	[192]
PEI	25 kDa	Graphen and Ag	*E. coli*, *S. aureus*, A. baumannii, S. sonnei, A. fumigatus and C. albicans	Excellent durability and electropositivity in physiological solutions, demonstrating significantly greater antimicrobial efficacy	[193]
	25 kDa	Ag	*S. aureus* and *K. pneumoniae*	Good antimicrobial activity	[194]
	1.8 KDa	Polyhyaluronic acid particles	*E. coli*, *S. aureus* and B. subtilis	Very effective against gram-negative and gram-positive strains of bacteria.	[195]
	2 KDa	Ag	S. epidermidis, *E. coli*, *S. aureus* and C. albicans	Stronger antibacterial activity	[196]

conclude that these nanoparticles could one day be an enticing therapeutic choice for bacterial infection care. The essential parameters for Ag NPs antibacterial activity are the Ag concentration, nanoparticles shape, size, stability, and accessibility. Because

of the importance of antibacterial agents' safety, several studies have documented potential toxicity of Ag NPs *in vivo* and *in vitro* [197].

As many polar terminal groups are localized inside a relatively thin shell of the macromolecules, the cations of dendrimer carboxylate salts can have an exceptionally high local concentration of Ag. The accessible tertiary nitrogens in the interior will simultaneously give rise to stable complexes with transition metal ions, such as Ag. Via guest-host interactions, PAMAM can solubilize many organic materials that are typically considered insoluble in water. For this purpose, bioactive materials, including metals, metal ions, and organic molecules, can be combined in one nanoscopic delivery vehicle using PAMAM dendrimers in varying quantities and shapes [177].

PEI-capped Ag nanoparticles were reportedly synthesized in sodium borohydride and PEI at room temperature. PEI fragments containing amine groups can provide a positive charge and stabilization to nanoparticles against agglomeration. In the synthesis of metal nanoparticles, PEI molecules serve as both a reductant and a stabilizer. Stable AgNPs can be readily prepared directly from an amine-containing aqueous solution with polyelectrolyte without reducing agents by a thermal phase. The findings demonstrated strong antimicrobial activity and cytotoxic effects of PEI-AgNPs [194].

Surfaces and bulk of modified materials with ATDPs have demonstrated bactericidal properties. These materials are the principal components for biomedical applications of various types of membranes or scaffolds. There were mainly two antibacterial mechanisms, including a) some molecules entered the cell by surface penetration and adsorbed cytoplasm anions to interfere with normal cell physiological behavior, i.e., to hinder bacterial growth and b) once bacterium ingested certain molecules; it could easily be stopped from exchanging materials with the outside [198]. In 2016 chitosan hydrogels were successfully prepared with chitosan and PAMAM dendrimer by glutaraldehyde acting as a crosslinking agent. The findings showed that PAMAM G2 dendrimer was an outstanding candidate for improving the antibacterial hydrogel function, which has plentiful classes of amines relative to other molecules or materials and does not cause antibiotic resistance in bacteria. The antibacterial effects were caused by the amine groups ($-NH_2$) with the bacteria. The results revealed that the addition of PAMAM greatly enhanced the chitosan hydrogel's antibacterial function. It also suggested that PAMAM's blending ratio was one of the most important factors impacting antibacterial activity [180].

Other studies have investigated combining polycationic modified PEI and polyanionic hyaluronic acid for interesting new synergic applications, such as antimicrobials and powerful antioxidant and anticancer content. New properties for polyhyaluronic acid-PEI, such as antibacterial activity, were obtained after modification. The findings revealed that the highest minimum bactericidal concentration value was 0.5, 1 and 0.5 mg/mL for *Escherichia coli*, *Staphylococcus aureus*, and Bacillus subtilis species at 72 h incubation time for 1:0.5 ratio of polyhyaluronic acid-PEI. Besides, the particles were shown to be biocompatible with L929 fibroblast cells and, surprisingly, cancer cell growth was found to be impaired based on the volume of PEI [195].

Viruses and the diseases they cause are no less critical than bacteria. However, identifying small molecules and effective vaccines to treat antivirals is difficult and time-consuming. One of the types of nanomaterials used in this field is ATDPs [199,200]. The structural probabilities of nanostructure complex formation between PAMAM and some drugs that suppress hepatitis virus growth, including Adefovir, Entecavir, Telbivudine, Lamivudine, Tenofovir, were investigated theoretically [201]. The researchers discussed an imaginary separation procedure of therapeutic agent mixture samples that inhibited the *in vitro* growth of a hepatitis virus. The results indicated that compounds Adefovir and Entecavir could be collected using PAMAM, and Telbivudine, Lamivudine and Tenofovir could be separated from the mixture of medicines.

5. Cytotoxicity of amine-terminated dendritic polymers

One of the drawbacks of using ATDPs to modify biomaterials is its toxicity, which has already been studied. In the following, we will briefly address the toxicity contributing factors and the methods to be overcome.

Regardless of the dendrimers' properties, which are interesting for biomedical applications, toxicity associated with terminal groups and multiple surface charges limits their clinical applications [202]. As shown in Table 5, factors such as cytotoxicity, hemolytic activity, complement activation, endocytic absorption and intracellular fate, biodistribution, general toxicity, immunogenicity, and the effect of dendrimers on cytokine and chemokine must be considered in assessing the biocompatibility of dendrimers [203]. Dendrimers used in the biomedical application should be biocompatible, safe, non-immunogenic, useful for therapeutic and imaging purposes, with high therapeutic windows, and precisely controllable structures. However, the main disadvantages existed in this way including, lack of knowledge of the effects of dendrimers in biochemical pathways and processes in mammalian systems, lack of knowledge of the toxicity and exposure pathways, cost of development, and implementation issues. *In vitro* and *in vivo* characteristics of dendrimers, such as their biocompatibility from cells to tissues and their pharmacokinetic/pharmacodynamic behaviors, may be enhanced by chemical modifications that modulate the structure, architecture, and cellular interaction with dendrimers [204].

Several experiments have been reported using various cell lines, concentrations, incubation periods, and assay methods to determine cytotoxicity of dendrimers. These studies showed that dendrimer toxicity depends on the composition of core and/or branches, the surface group, the generation, and the concentration. The toxicity of dendrimers depends on the central structure but is more highly affected on the dendrimer surface by the functional groups [205]. Numerous studies have emphasized the crucial role that surface functional groups play in regulating cytotoxic properties. The most popular dendrimer production strategies with lower cytotoxicity are the use of polyethylene glycol (PEG[26]); PEGylation, use of carbohydrate engineered dendrimers; acylation, use of anionic dendrimers and grafting of amino acids, such as phenylalanine, and glycine or peptides (Table 5) [204]. Table 5 shows that an alternative approach to prevent toxicity is the preparation of dendritic structures based on biocompatible units, like those generated in established metabolic pathways.

The positively charged surface functional groups of ATDPs are responsible for the toxicity and destabilize the cell membrane and cause cell lysis [206]. Membrane permeability has been greatly improved by the most positively charged polymer mass, while ATDPs' membrane permeability came from its circular nature, facilitating its associations with lipid membrane cells and then cell death. Simple modifications of the terminal surface groups can decrease toxicity levels. Nitrogen functions with lower basicity exhibit lower cytotoxicity due to their reduced cell membrane interactions. There have been no reports of systemic analyses of the generation-dependent toxicity applying to higher and lower levels. However, several studies have recorded a lower degree of cytotoxicity in the lower generations of amine-terminated dendritic

[26] Polyethylene glycol.

Table 5
Dendritic polymers toxicity issues and the solution of them [202].

Dendritic polymers toxicity	Solutions for toxicity issues	
	Biodegradable/biocompatible dendrimers	Surface engineered dendrimers
• Cytotoxicity • Hemolytic toxicity • Haematological toxicity • Immunogenicity • *In vivo* toxicity	➢ Polyether dendrimers ➢ Polyester dendritic ➢ Polyether imine dendrimers ➢ Polyether−copolyester dendrimers ➢ Phosphate dendrimers ➢ Citric acid dendrimers ➢ Melamine dendrimers ➢ Peptide dendrimers ➢ Triazine dendrimers	✓ PEGylation ✓ Carbohydrate engineered dendrimers ✓ Acetylation ✓ Half generation- or anionic dendrimers ✓ Amino acid or peptide conjugated dendrimers ✓ Drug and DNA/gene conjugated dendrimers ✓ Antibody functionalized dendrimers ✓ Tuftsin conjugated dendrimers. ✓ Folate-conjugated dendrimers ✓ Miscellaneous

formation. For example, systematic studies of the structurally similar PPI dendrimers showed that the lower generations (G0−G2) are passively rather than actively uptaken and are non-toxic to mammalian cells, suggesting the importance of the mechanism for cellular uptake [207].

It was reported the effect of PAMAM G2−G4 dendrimers on Caco-2 cell viability *in vitro*. The growth in cationic generation decreased cell viability, and this viability decreased with the concentration of cationic PAMAM dendrimers for a considered generation. The same authors have documented the effect of concentration and generation of PAMAM dendrimers (G2, G4, and G6) on cell growth and cytotoxicity in HEK293 T and HeLa cell lines [208]. The other research details the *in vitro* viability of Caco-2 cells in response to N-acetylated G2−4 PAMAM dendrimers [209]. As the number of acetylated amino groups on the surface increased, cell viability decreased.

Interestingly, when Kissel and colleagues [210,211] examined the cytotoxicity of a series of polycations in L929 mouse fibroblasts (lactate dehydrogenase release control and viability evaluation using the 24 h MTT assay), they reported limited toxicity to PAMAM G3. It is interesting, though, that the polymer solutions were re-adjusting back to physiological conditions to remove any polymer-induced improvements in medium osmolarity and pH in these studies. One may argue that such modification does not apply to the *in vivo* situation where pH and osmotic effects cannot be removed. These authors rated the polymer cytotoxicity order as PEI > dextran > PAMAM G3 and reported a strong association between the release of lactate dehydrogenase, their cell viability indicator of MTT, and changes in cell morphology visualized by light microscopy.

PEI is well established as the gold standard approach to cell transfection, and clinical trials are currently studying several PEI derivatives. High-molecular weight PEIs such as high-generation PAMAM dendrimers have high gene loading and transfection performance but are usually followed by significant cytotoxicity and cargo release difficulties. The last research in 2020 found that the surface modification of low-molecular weight PEI and low-generation PAMAM with PEG had the highest effectiveness in the transfection of Jurkat cells and had low cytotoxicity [212].

Another beneficial technique for producing less toxic dendrimer is surface engineering, alongside the development of biocompatible dendrimers. Surface engineering in dendrimers is a process of changing the dendrimers' surface with various functional groups to mask the cationic charge of the dendrimers. It is the process that could turn cytotoxic dendrimers into biocompatible dendrimers. Different surface engineering techniques such as PEGylation, acetylation, folate conjugation, carbohydrate, peptide, drug, gene, and tuftsin conjugated, anionic, and antibody functionalized dendrimers have supported this. Surface modification of dendrimers leads to the protection of surface amine groups and reduces dendrimers' inherent cytotoxicity [202]. In addition to reducing the inherent toxicity of dendrimers, functionalization often imparts specific other useful properties for its use as a drug delivery system. This involves improving the drug encapsulation performance, enhancing biodistribution, pharmacokinetic properties, increasing solubility, targeting the right site, increasing transfection quality, continuous and regulated drug release, and raising the stable profile and improving the therapeutic potential as an antiviral, antibacterial action [202].

6. Conclusion and future trend

Amine-terminated polymers have been used as promising nanomaterials in biomedical engineering among various kinds of dendritic polymers. Therefore, polyamidoamine, polypropyleneimine, and polyethyleneimine were briefly identified as ATDPs, and their application for diagnostic and therapeutic agents modification in six major fields, including drug delivery, gene transmission, biosensor, bioimaging, tissue engineering, and antimicrobial action were described.

There are some benefits of using dendrimers to modify DDS, such as decreasing the necessary dosage of a drug, improving the effectiveness of the medication, regulating drug biodistribution, decreasing drug side effects, improving targeted drug delivery, fast detection with fluorescent tests, incorporating several routes of administration and high drug-loading capacity. Also, to boost the shortcomings of gene delivery systems, ATDPs containing large numbers of primary amine surface or internal and tertiary amine classes are emerging as promising non-viral vectors for the delivery of genes. They are non-immunogenic and are as successful in modifying other vectors as cationic polymers are believed to transfer genes through the process of proton sponge.

The dendrimers have several conjugation sites, a tightly functionalized and structurally robust architecture that turns them into novel nanomaterials for biosensor device modifications. The specific properties of dendrimers, especially ATDPs, make them an ideal platform for covalently linking multifunctional imaging targeting ligands. This means that by integrating the surface functionality of the dendrimers and special molecular recognition capabilities with the properties of bioimaging agents, various drawbacks that are excited in this area can be modified.

The unique characteristic of ATDPs makes them promising candidates for various tissue engineering applications such as crosslinking agents, surface charge modulators, and primary components in scaffolds' structure to emulate extracellular matrices. Hydrophobic branched in dendrimers allows their penetration into the phospholipid bilayer contributing to bacterial membrane disintegration. Besides, due to the antimicrobial effects of ATDPs,

they may be used to modify other products such as antibiotic drug distribution, antibacterial nanoparticles, and functionalization of substances.

For biomedical applications, non-toxic dendrimers are mandatory for their therapeutic advances. The two major toxicity avoidance techniques for dendrimer are focused on the design and synthesis of a biocompatible center and branching units, masking peripheral charges using approaches to surface engineering.

These novel characteristic of ATDPs reveal huge potential for bulk and surface modification of various kind of biomaterials including films, fibers, membranes, scaffolds, nanoparticle, biosensors, bioimaging agents and antimicrobial components in future.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution

M. Delyanee performed the curation of literature and wrote the main paper. S. Akbari supervised the work and edited the manuscript. A. Soulok have read and approved the final manuscript.

Declaration of competing interest

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

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