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A Review on Dendrimers: A Novel Drug Carrier in Oncology

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HUMAN

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ABSTRACT

Among all the recent advances of nanotechnology, dendrimers have been emerging as a highly attractive class of drug delivery for tumor therapy. Dendrimers are multifunctional smart Nanocarriers which can deliver one or more therapeutic agents selectively and safely to cancer cells. The presence of functional groups in the outer surface of the dendrimers will permit other moieties that can actively target particular diseases that are currently used as tumor-targeting strategies. The therapeutic use of the dendrimers is contributed by drug encapsulation, solubilization, and passive targeting and active targeting. Dendrimers are used as ideal carrier vehicles on cytotoxicity, biodistribution, blood plasma retention time, and tumor uptake. In this review, we highlight the advantages of dendrimers over conventional chemotherapy and recent advances in drug delivery by various types of dendrimers for Cancer therapy and its diagnostic applications.

INTRODUCTION

Cancer is a killer disease. Almost all cells in the body are susceptible to cancer, and more than 200 distinct varieties of cancers have been described. Most varieties of cancer are rare, and deaths due to cancer are mainly attributable to only a few common ones such as lung, breast, colon, skin, and blood cancers. Cancers are classified according to the type of tissue and type of cell in which they originate. For example, if the disease is believed to have originated within the tissues of the breast, the diagnosis may be breast cancer. Though there is significant progress in the field of anticancer technology, we are still badly in need of a reliable cure for malignant growths. At present, a variety of drug delivery approaches including polymer microcapsules and microspheres, liposomes, polymer conjugates, and nanoparticles are either FDA-approved or are in clinical development as cancer treatments. The success of novel strategies for cancer therapy relies strongly on the development of reliable delivery devices capable of improving the therapeutic index of biologically active molecules. During the last few decades particularly, medical science has witnessed the exploration of several delivery devices, and along with a multitalented versatile star named "dendrimers" is currently visible on the horizon. [1]

DENDRIMERS

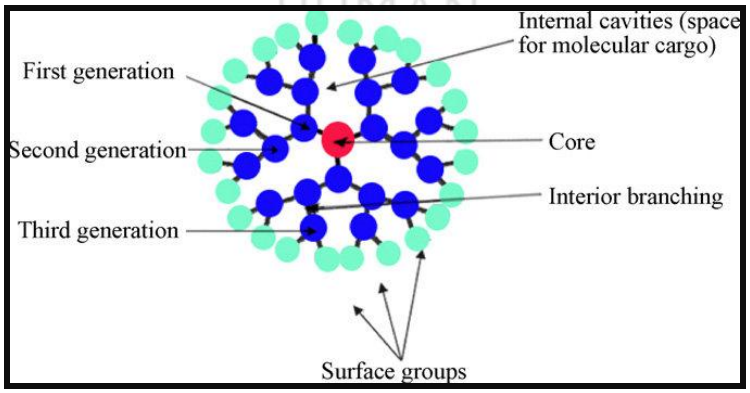

Figure No. 1: General representation of the model structure of a dendrimer

Dendrimers are hyperbranched molecules that were first discovered by Fritz Vogtle in 1978. The word "dendrimer" originated from two words, the Greek word "dendron" meaning tree, and "meros" meaning part or unit. These might also be called as 'cascade molecules', but this term is not as much established as 'dendrimers. Dendrimers are nearly monodispersed macromolecules that contain symmetric branching units built around a small molecule or a

linear polymer core. Polyionic dendrimers do not have a definite shape and undergo changes in their size, shape, and flexibility as a function of increasing generations. [2]

Dendrimers are synthetic macromolecules with a tree-like and well-defined branched structure. Recently, progress has been made in the application of biocompatible dendrimers for the treatment of cancer, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin. Bifunctional polyamidoamine (PAMAM)-based dendrimers are used because they selectively target cancer cells.

Dendrimers have successfully proved themselves as useful additives in different routes of drug administration because they can render drugs of greater water solubility, bioavailability, and biocompatibility. These carriers have well-defined molecular weights and host-guest entrapment properties. Since dendrimers are synthesized from branched monomer units in a stepwise manner, it is possible to conduct precise control on molecule size, shape, dimension, density, polarity, flexibility, and solubility by selective different branching units and surface functional groups.

Dendrimers possess empty internal cavities and open conformations (for low-generation dendrimers), which make it possible to encapsulate hydrophobic drug molecules. Besides, they have a much higher surface functional group density when compared with conventional macromolecules. These functional groups permit the application of dendrimers to enhance the solubility of many drugs. [3]

Applications have included solubility enhancement, RI contrast agents, neutron capture therapy, gene therapy, drug delivery, nanocomposites, and photodynamic therapy. In the present review, we have summarized the work done with dendrimers in the field of cancer therapy, ranging from solubilization to hybrid dendrimer mediated targeting for cancer therapy.

STRUCTURE OF DENDRIMERS

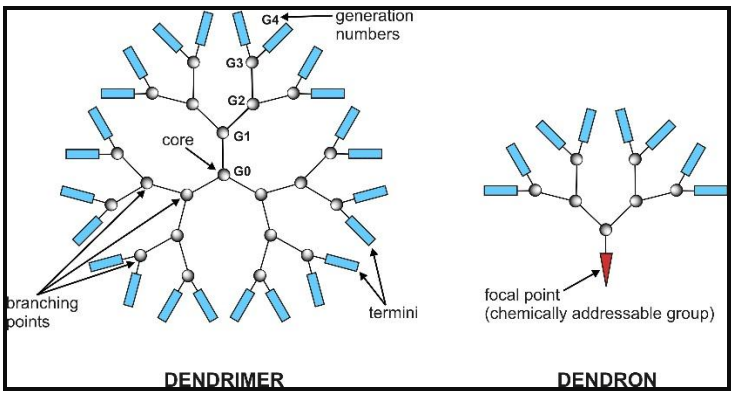

Figure No. 2: **Structure of dendrimer with different generation (G-0 to G4)**

- An inner core
- Interior layer composed of repeating units radically attached to cores.
- The Exterior layer is attached to the interior generation.

IDEAL PROPERTIES OF DENDRIMERS

Apply dendrimers as tools for drug delivery devices in vivo, they have to fulfill several biological demands of crucial importance. The minimization of side effects of the drug can be altered by modifying the properties of the carrier [4]. The ideal dendrimers should be:

- Inert and non-toxic
- Biodegradable and Non-immunogenic
- Able to cross the barriers such as intestine, blood-tissue barriers, cell membranes.
- Able to focus on to specific structures,
- Compatible with guest molecules,
- Must protect the drug until it reaches the desired site of action and releases the drug.

PHYSICOCHEMICAL PROPERTIES OF DENDRIMERS

Many of the properties of dendrimers make them suitable for pharmaceutical applications which are as follows:

- Nanoscale sized that have similar dimensions to important bio-building blocks, such as proteins, DNA, etc.

- Nanoscale improves the pharmacokinetic and pharmacodynamics properties of a drug so that there is also an increase in bioavailability.

- Multiple numbers of terminal surface groups (Z) suitable for bio-conjugation of drugs, signaling groups, targeting moieties, or biocompatibility groups.

- Surfaces may be designed with functional groups to augment or resist transcellular, epithelial, or vascular biopermeability.

- Interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties.

- Surface groups that can be modified to optimize bio-distribution; receptor-mediated targeting, therapy dosage, or controlled release of drug from the interior space.

- Have an ability to get excreted from the body as a function of nanoscale diameter.

- The size and molecular mass of dendrimers can be specifically controlled during synthesis which cannot be done for linear polymers.

- These carriers have a significantly lower viscosity than linear polymers. These have high solubility, miscibility, and reactivity due to the presence of many chain ends.

- These carriers possess solubility in a large number of solvents. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. [5]

PREPARATION

Dendrimers are generally prepared by 2 methods - the divergent method and convergent method. There is a fundamental difference between these 2 construction concepts.

D**ivergent methods**: Dendrimer are grows outward from a multifunctional core molecule. The core molecule reacts with monomer molecules containing 1 reactive and 2 dormant groups giving the first-generation dendrimer. Then the new periphery of the molecule is activated for reactions with additional monomers. This method is continued for several

generations and a dendrimer is built layer after layer. The divergent approach is successfully assembled for the production of large quantities of dendrimers. Problems have mainly occurred from side reactions and incomplete reactions of the end groups that lead to a defect in structure. To prevent side reactions and incomplete reaction, excess of reagents is needed. [6]

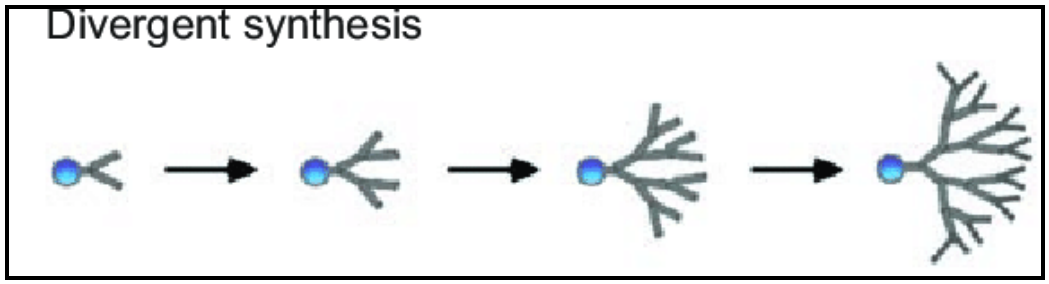

Figure No. 3: **Divergent method of dendrimer synthesis**

Convergent methods: They are developed as a response to the weaknesses of the synthesis of dendrimers from the divergent method. In the convergent approach, the dendrimer is constructed by stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms referred as dendrons, they are attached to a multifunctional core molecule. It is relatively easy to purify the desired product. Convergent methods are mainly used to minimize the defects in the final structure. [7]

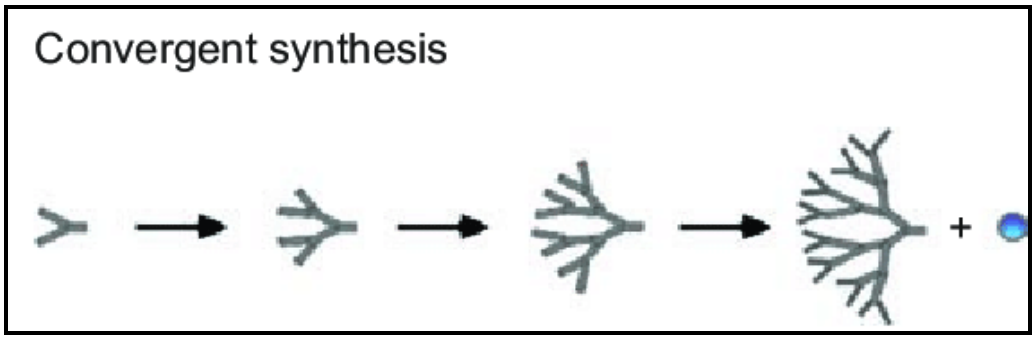

Figure No. 4: Convergent method of dendrimer synthesis

FACTORS AFFECTING DENDRIMERS SYNTHESIS

Different factors might affect dendrimer synthesis. The non-ideal dendrimer expansion may be manifested through different ways which include: [8]

1. Incomplete addition reaction.

2. Intermolecular cyclization.

3. Fragmentation.

4. Solvolysis of terminal functionalities

TYPES OF DENDRIMERS

- **PAMAM (Poly Amido Amine) Dendrimer:** These are spheroidal or ellipsoidal in shape. It has high solubility and reactivity due to the incidence of a number of functional end groups and empty internal cavities. Synthesis: Divergent

- **PPI (Poly Propylene Imine) Dendrimer**: Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as the center. These are commercially available up to G-5 and are extensively used in material science and biology. Synthesis: Divergent

- **Chiral Dendrimer:** The chirality of the dendrimers was based upon the building of constitutionally different but chemically alike branches to the chiral core. Synthesis: Convergent

- **Multilingual Dendrimers**: These are the dendrimers that hold multiple copies of a particular functional group on their surface. Synthesis: Convergent.

- **Tecto Dendrimers:** These were made up of core dendrimers, which can be surrounded by other dendrimers, which execute a specific function leading to a smart therapeutic system used to diagnose the diseased state and deliver API to the accepted diseased cell. Synthesis: Divergent

- **Hybrid Dendrimers**: These dendrimers have characteristics of both dendritic and linear polymer. Synthesis: Divergent

- **Amphiphilic Dendrimers:** These have one half that is electron-donating and another half is electron retreating. Synthesis: Divergent

- **Peptide Dendrimers**: Peptide dendrimers are those which hold amino acid as branching or interior unit. These are commonly used for diagnostic purpose and for the delivery of the vaccine. Synthesis: Convergent

- **Frechet-Type Dendrimers:** These were based on poly benzyl ether hyperbranched skeleton. The carboxylic acid group attached to the surface of the dendrimers that provides a

site for further functionalization and to improve the solubility of dendrimers. Synthesis: Convergent

- **PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers:** These are silicon containing commercial dendrimers which are inverted unimolecular micelles and contain exterior hydrophobic organosilicon and interiorly hydrophilic, nucleophilic. Synthesis: Convergent and Divergent

- **Multiple Antigen Peptide Dendrimers**: These are dendron-like molecules. Their assembly is mainly based upon the polylysine frame. Lysine with its alkyl amino side-chain performed as an excellent monomer for the overture of frequent branching points. Synthesis: Convergent and Divergent. [9]

CLASSIFICATION

Table No. 1: Classification of Dendrimers

Sr. No.	Classification of dendrimer	Application/Methods
1.	Simple Dendrimer	They have simple monomer units. These materials consist of 4, 10, 22, and 46 benzene rings linked symmetrically.
2.	Liquid crystalline dendrimer	These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer.
3.	Chiral dendrimer	In chiral dendrimers, the chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core.
4.	Micellar dendrimer	These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a collection of the aromatic polymeric chain.
5.	Hybrid dendrimers	These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form.
6.	Amphiphilic dendrimer	These are the class of globular dendrimers that have an asymmetrical but highly controlled division of chain-end chemistry.
7.	Metallo dendrimer	Dendrimers are attached with the metal ion to form the complexation either in the interior or on the peripheral.

MECHANISM OF DRUG LOADING

Different mechanisms of drug loading are explored, and they are broadly subdivided into 3 types: simple encapsulations, electrostatic interactions, and covalent conjugations. [10]

- **Simple Encapsulation:** The ellipsoidal or spheroidal shape, empty internal cavities, and open nature of the design of dendrimers make it possible to directly encapsulate guest molecules into the macromolecule interior. These empty internal cavities are hydrophobic in nature, which are suitable to interact with poorly soluble drugs through hydrophobic interactions.

- **Electrostatic Interaction**: The high-density functional groups such as amine groups and carboxyl groups on the surface of dendrimers have potential applications in increasing the solubility of hydrophobic drugs by electrostatic interaction. For example, G3 PAMAM dendrimer with an ammonia core is used. It has higher amino group density when compared with other classical linear polymers.

Covalent Conjugation: The presence of enormous numbers of the functional groups within the surface of dendrimers makes it appropriate for the covalent conjugation of various drugs with relevant functional groups. In this case, the drug is covalently bound to the dendrimers and the release of the drug occurs via chemical or enzymatic cleavage. [11]

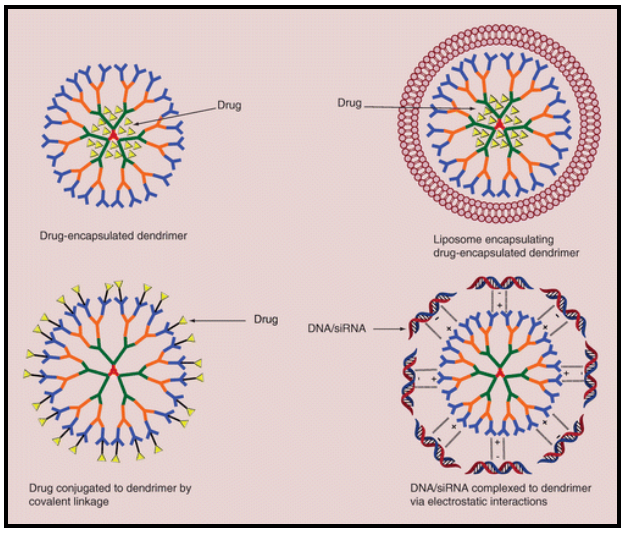

Figure No. 5: **Different mechanism of drug loading**

ADVANTAGES OF DENDRIMERS OVER CONVENTIONAL ANTI-CANCER AGENTS

- High drug loading capacity
- Nano-sized dendrimers are used for pre detectable release profiles, favorable pharmacokinetics, and targeting potentials.
- Dendrimer increases the solubility of poorly soluble anti-neoplastic drugs.
- Clearance is reduced through the Reticuloendothelial system due to its nano size.
- Multiple functional groups are present on the outer surface of the dendrimers.
- The presence of various peripheral functional groups on dendrimers is responsible for tumor cell-specific delivery. [12]

DISADVANTAGES

- Incomplete chemical reaction
- Intermolecular cyclization
- Fragmentation
- Solvolysis of terminal functionalities

CHARACTERIZATION OF DENDRITIC POLYMER

- Spectroscopy
- Scattering techniques
- Microscopy
- Physical properties
- Solubility and Rheology
- Electrical Techniques
- Determination of Melting Point

- Elementary Analysis

DRUG DELIVERY BY VARIOUS TYPES OF DENDRIMERS

The utility of dendrimers may be renowned by their ability to transverse several delivery barriers using two principles- active tumor targeting and passive tumor targeting.

Passive tumor targeting-utilizes the EPR impact that involves dendrimers to extravasate and accumulates selectively within the cancer tissue. [13]

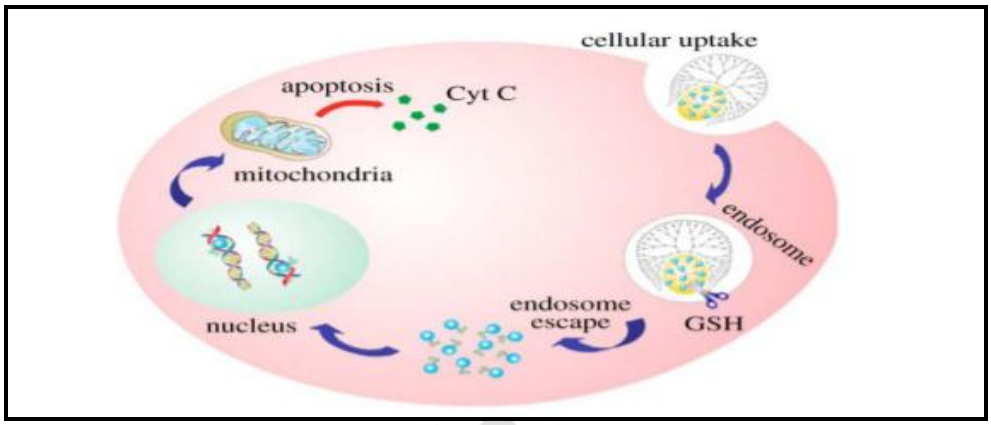

Figure No. 6: **Cellular uptake of the drug from dendrimers by passive targeting**

➢ Active targeting: Active tumor-targeting- It involves conjugation of specific targeting ligands on nanocarrier surfaces that will facilitate their selective binding to overexpressed receptors on specific tumor cells.

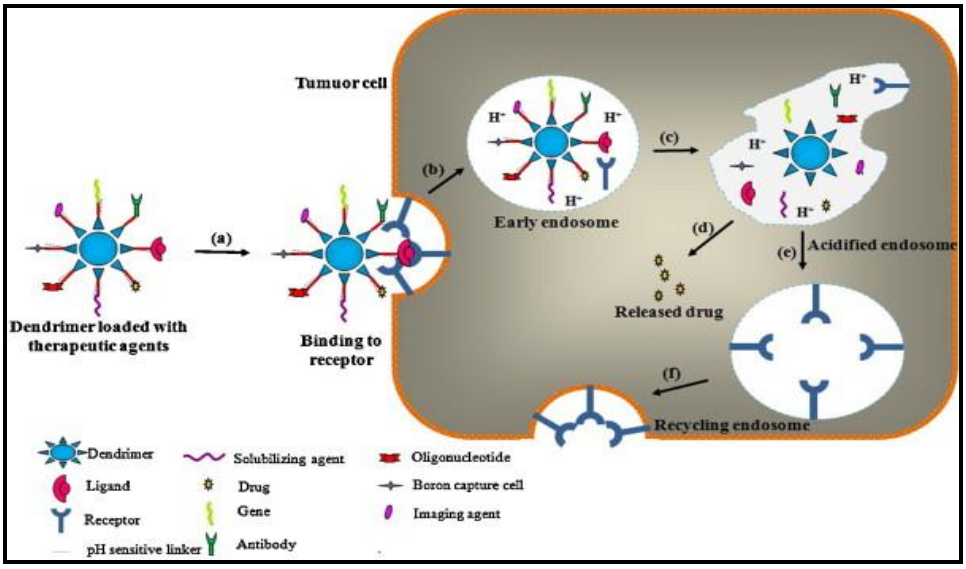

Figure No. 7: Cellular uptake of the drug from dendrimer by active targeting

Moreover, a Passive targeting approach effect applies only to the highly permeable solid tumors. However, the permeability of different types of tumors is very low or non-uniform throughout heterogeneous tumors. These shortcomings may be resolved by an Active targeting approach that permits conjugation of a variety of cancer targeting.[14]

DENDRIMERS IN CANCER THERAPY

1. Drug Conjugated Dendrimers in Cancer Therapy: Polymeric drug conjugates have several advantages over free drugs, among them being increased plasma half-life, decreased drug resistance, and linkage-tuned drug release. An alternative strategy for utilizing dendrimers as anticancer drug carriers is to make the most of their well-defined multivalent structure in covalent attachment of drug molecules to their periphery.

Table No. 2: List of conjugated dendrimers employed in cancer therapy

Sr. No.	Type of scaffold	Bioactive studied	Purpose/outcomes of the study
1	Cyclic core	5-fluorouracil	Enhance water solubility, achieve selective slow release and reduce toxicity
2	PAMAM	Cisplatin	Solubility enhancement, decrease systemic toxicity, and selective tumor accumulation
3	Polyester	Doxorubicin	Selective delivery of the drug via a pH-sensitive linkage
4	ST-PHPMA-PAMAM star-copolymer	Doxorubicin	Achieve enzyme-mediated slower drug release, diminishing drug cytotoxicity

PEGylated Nanocarriers in Cancer Therapy: In cancer therapy, PEGylated dendrimers are a class of nanocarriers that are capable of effectively delivering high drug payloads relatively unharmed to attack cancer. PEGylated dendrimers not only drastically augment drug loading and solubilization, but also eliminate the naked dendrimer scaffold drawbacks of hemolytic toxicity, uncontrolled drug outflow, macrophage uptake, short half-life, etc. [15]

- **PEGylated Dendrimers: A Way to Achieve Solubilization and Controlled Release of Chemotherapeutics:** A poorly water-soluble anticancer candidate manifests several in vivo consequences: hampered bioavailability, raised probability of food effect, unfinished release

from the formulation, and also greater interpatient variability. PEGylated dendrimers are an innovative class of dendrimers with the advantage of additionally attached PEG-chains, which enhances their solubilization ability and augments surface crowding and thereby enables controlled release of drug from the dendrimers' scaffolds. [16]

- **PEGylated Dendrimers:** In Maintenance of *in Vivo* Stability

Dendrons based on aspartic acid units and arabinofuranosyl cytosine (Ara-C) conjugated via its amine group by various linkers including amides and carbamates are prepared. This strategy improved the *in vivo* stability, the blood residence time of the drug, and increased its stability.

Table No. 3: PEGylated dendrimers employed against cancer

Sr. No.	Type of scaffold	Bioactive studied	Purpose/outcomes of the study
1	PEGylated PAMAM	MTX/Adriamycin	Solubilization and sustained release benefits
2	PEGylated PAMAM	TU-DTPA	Assess blood residence and biodistribution pattern
3	PGDs	Paclitaxel	Solubilization was more in the case of PGDs as compared to PEG_{400}, a frequently used solubilizing agent
4	PEO-dendrimer hybrids	Ara-C	To improve *in vivo* stability, blood residence time and drugs stability
5	PEO-dendrimer hybrids	Doxorubicin	To have a long-circulating, in vivo stable, pH-responsive drug releasing carrier

- **PEGylated Dendrimers: Toward Augmentation of Biocompatibility of Anticancer Drugs and the System:** Dendrimers possess great potential as drug delivery devices for cancer chemotherapy. While comparing the cationic and anionic dendrimers, Cationic dendrimers were found to be more cytotoxic and hemolytic than anionic. These nanoparticles were also found to be efficient in reducing drug leakage, hemolytic toxicity, and renal filtration while raising *in vivo* stability and biocompatibility.

2. Liposomal "Locked in" Dendrimers: Liposomes, the most extensively studied system for drug delivery, have already been comer canalized since formulations of doxorubicin, amphotericin B, and cytarabine are in the market now, and many others are in the clinical

phase. The use of dendrimers as modulators were incorporated into liposomes for the release of drugs. [17]

3. Glycodendrimers in Cancer Targeting: The special biology of carbohydrate receptors contains clustered so to attain biologically meaningful affinities for the receptors. Glycodendrimers are constructs having several surface carbohydrate residues accessible for multiple binding interactions. They are chemically and geometrically well-defined monodisperse macromolecules, that are suitable as tools for medicinal and pharmaceutical purpose.

4. RGD-Coupled Dendrimers in Antiangiogenic Therapy: Antiangiogenic therapy is yet another approach for dealing with cancer that involves the prevention of neovascularization by inhibiting proliferation, migration, and differentiation of endothelial cells. Tumor-induced angiogenesis is a consequence of ligation by extracellular matrix proteins to the alpha-v-beta-3 integrin, which is highly expressed on many tumor cells. The alpha-v-beta-3 integrin is one of the most specific of these exclusive markers, which is found on the luminal surface of the endothelial cells only during angiogenesis. [18]

5. Antibody/Ligand Guided Dendrimers: Antibodies are excellent targeting tools because of their intrinsic ability to undergo feedback with a specific target. Antibodies can work against a tumor in several ways: they can either combine with specific antigens on the surfaces of malignant cells and make them susceptible to destruction by immune cells of the host, or they can direct them to self-destruct.

6. Dendrimers in Boron Neutron Capture Therapy (BNCT): Boron neutron capture therapy (BNCT) is a binary approach to the treatment of cancer. For boron neutron capture therapy to be effective in curing cancer, a minimum B concentration of 10-30 µg/g of tumor must be selectively delivered to the tumor**.**

7. Dendritic Architecture in Optical FluorescenceImaging: Current progress with numerous biocompatible fluorescent molecules suggests that tumor biosensing could be perfected by using fluorescence detection techniques. These approaches would have additional advantages over other no biocompatible techniques such as radiation or chemical analysis. [19]

APPLICATION[20]

- **Dendrimers in the biomedical field:** The dendritic polymers are analogous to protein, enzymes, and viruses and can be functionalized. Dendrimers and other molecules are attached to the periphery or encapsulated in their interior voids for increasing the action.

- **Dendrimer as magnetic resonance imaging contrast agents**: Dendrimer contains metal chelates that act as a magnetic resonance imaging contrast agent. Dendrimers are extremely suited and used as image contrast media because of their properties.

- **Dendrimers as Bio mimics:** Dendrimers with macromolecular dimensions and compartmentalized structure are ideal mimics for a wide variety of biomolecules. The commercially available dendrimers provide to make microenvironments.

- **Dendrimers in targeted drug delivery:** Targeted drug delivery is the method of introducing medicine to the patient in a manner that will increase the concentration of medication in a particular part of the body. Dendrimers have multifunctionality and a high potential for drug delivery because of their high density and a wide variety of functional groups on their surface.

- **Dendrimers in transdermal drug delivery**: To improve the effectiveness of drugs, transdermal drug delivery system has come into existence long back. Drug delivery through the skin to achieve a systematic effect of the drug is referred to as transdermal drug delivery.

- **Dendrimers in oral drug delivery**: Oral drug delivery is the most popular in the pharmaceutical field because of ease of production, low cost, convenience of administration, and flexibility in designing the dosage form.

- **Dendrimers in ocular drug delivery**: The topical application of active drugs into the eye is the most prescribed route of administration for the treatment of ocular disorders.

- **Dendrimers in pulmonary drug delivery**: By measuring the plasma anti-factor Xa activity using PAMAM dendrimers will increase the pulmonary absorption of the drug Enoxaparin.

CONCLUSION

Nowadays understanding the disease, development of newer targeted therapies, and treatment for different types of cancer remains a major challenge. Among all the latest developed Nanotechnologies, Dendrimer mediated drug delivery has been emerged as a superior opinion to overcome the disadvantages and shortcomings of conventional chemotherapy in cancer treatment. Dendrimer act as a carrier for the delivery of the drug to the tumor by the methods such as encapsulation and conjugation. The dendrimers mediated drug delivery into the site of the tumor mostly occurs through PAMAM, PPI, and PLL by passive targeting or by active targeting. Several advances have been made to obtain safe and efficacious dendrimer-based formulation for increasing the specificity and efficacy towards the diagnosis, prevention, and treatment of cancer. The future scope of dendrimers in research depends on its relevancy in areas like synthesis, drug delivery, biotechnology, nanotechnology, detection, catalyst, and cosmetics.

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