Dendrimers: A Potential Carrier for Cancer Therapy

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Abstract

A key problem in medical research is cancer therapy. Numerous new nanotechnologies are being explored for cancer therapy and diagnosis. Among these, dendrimers are highly potential class of drug delivery vector for cancer treatment because of their distinctive qualities, such as high degree of branching, self-assembling, chemical stability, low toxicity, high aqueous solubility, polyvalency, mono dispersity and biocompatibility. Acetylation, PEGylation, Glycosylation, and Amino Acid Functionalization can be used to increase the biocompatibility of dendrimers to assure safety for the normal cell. These properties of dendrimers display a reproducible pharmacokinetic behaviour that could ensure biodistribution and efficacy. Dendrimers are hence being taken advantage of as a nanotheranostic platform which incorporate a different class of therapeutic, imaging, and focusing on cancer treatment. As well as these features have made an advanced application in pharmaceutical and medicinal chemistry. Dendrimers are nanosized, branched polymeric molecule with having well defined homogenous and monodispersed structure. In dendrimers, the atom and group of atoms are surrounded by a branch which is termed as dendrons. Dendrimers have three distinctive structural parts incorporate with centre, branches (an inside layer made out of rehashing units connected profoundly) and terminal gatherings joined to the branches. Dendrimers can be used for treatment of variety of cancer and also used in various medicinal and practical application such as photodynamic treatment, boron neutron capture treatment, and quality treatment for malignant growth are being inspected. This present review briefly discussed the preparation of dendrimers and their possible applications in cancer therapy and biomedical fields.

Keywords: Cancer Therapy, Drug Delivery, Biocompatibility, Malignant growth, Dendrimers

1. INTRODUCTION

Malignant growth is one of the world's most upsetting infections with no treatment has been developed for curing of tumour cell in body[1]Finding new and innovative technique for cancer treatment is major problem across the world. Cancer is characterised by abnormal cell growth, maturation, loss of cellular growth, and disruption of homeostasis. Among all newly developed formulation about 30-40% of drug are lipophilic and fail to reach market due to their poor bioavailability or low water solubility. Traditional medicine having limited capacity to restrict the poor drug release, high toxicity,and less solubility. New nanomaterial-based medication delivery methods may provide a ray of hope for resolving these challenges. Nanotechnology is the application of science, design, and innovation to the nanoscale, which ranges from 1 to 100 nanometres. Nano technology play crucial role in biomedicine and targeted drug delivery system. Nano particle is a form of nano biomaterial which ranges 10 to 100nm. Nanomedicine is an important subfield of nanotechnology that aids in disease treatment and cure through nano formulation. One of the primary purposes of nanotechnology is to provide a secure, safe, effective, high-quality formulation for increasing the bioavailability of active pharmaceutical ingredients in body fluids[2,3]. In 1986 nanoparticles is used as drug carrier in cancer therapy. Due to having high specificity and accumulation with tumour tissue nano particle is very promising particulate for oncology. Dendrimers have been highlighted as promising nanostructures in Nanomedicine due to their distinct physio-chemical properties. Dendrimers are nanosized, homogeneous,mono dispersed structure with sizes varying from 1to 15 nanometre.Dendrimers having unique characteristics such as high degree of molecular uniformity less polydispersity, high level of compatibility due to this its widely used in chemical field application. Dendrimers recognized as high level of nanotheranostic platform that can possibly reform the oncology field by its unique and exciting features. Dendrimers based carrier are enhanced the oral bioavailability of poor water-soluble drug by altering their pharmacokinetic and pharmacodynamic property [4].Dendrimers are synthetic, branch structure polymeric molecules (Fig. 1). The term dendrimers originated form Greek work dendrons which means branching of a tree. Dendrimers also termed as cascade molecules. The structure of the dendrimers consists of 3 individual functional group such as COOH, COONA, NH2 or OH. Dendrimers also comprises of 3 components i.e., central core, repetitive branching unit and terminal group.

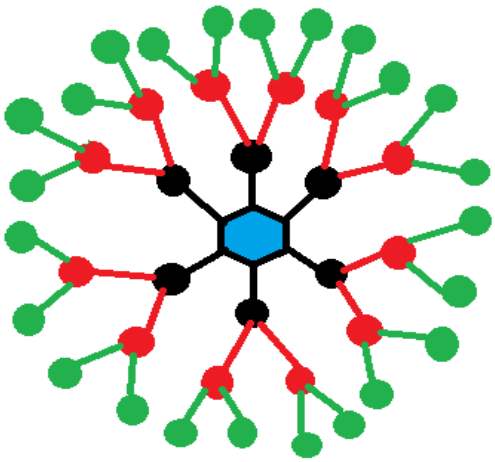

Fig. 1 Structure of Dendrimer

Fritz Vogtle and his co-worker introduced dendrimers in 1987 and in 1985 tomalia synthesized family of dendrimers which known as “newkomesgroup” [5].In 1990s dendrimers used in medical application. After many investigation and innovation dendrimers has been selected for treatment of cancer therapy because of their well-defined shaped and size [6]. Dendrimers a synthetic polymer plays important role in pharmaceutical drug development and discovery. Optical properties of dendrimers help to determine particle diameter and size[7].The advantage associated with dendrimer such as high loading capacity, reduce clearance through reticuloendothelial system, having appropriate nano sized which help for pre dectable numerous and high bioavailability. This review will be based on fundamental research in dendrimers for cancer therapy, and an assessment of these new developments will detail what advantages dendrimer-based therapeutics may have over conventional cancer drugs.

II. CLASSIFICATION AND TYPES OF DENDRIMERS

Dendrimer can be classification on the basis of their shape, structure, branching, solubility, chirality and attachment, which may be illustrated below:

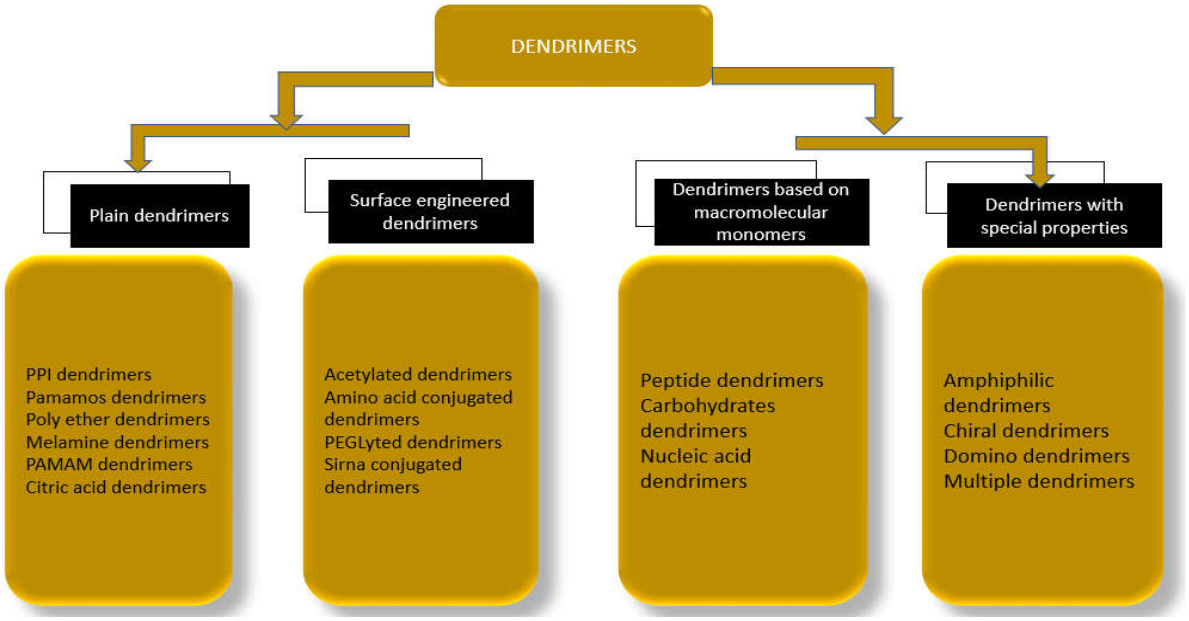

Fig.2 Types of dendrimers

2.1. DENDRIMER CLASSIFICATION: ON THE BASIS OF STRUCTURE:

a. Simple Dendrimers: These kinds of dendrimers comprise of basic monomeric units which depend on even replacement of benzene, tricarboxylic acid ester. Benzene ring symmetrically connected at position 4,10,22 and 46 and they have molecular diameter 45Å[8,9].

b. **Crystalline Dendrimers:** Mesogenic monomers generated by carbosilane make these dendrimers [10].

c) **Chiral Dendrimers:** The chirality of these dendrimers is determined by the structure of four intrinsically distinct but artificially comparable branches to a chiral centre, such as chiral dendrimers derived from pentaerythritol[11].

d) Micellar Dendrimers: These kinds of dendrimers are completely water soluble, aromatic, and hyper branched dendrimers. These polymeric chain helps to produce milieu which resulted that complex small organic molecule amphiphilic Dendrimers. Amphiphilic dendrimers are consisted of hydrophobic alkyl chain and hydrophilic poly(amidoamine)dendron. These dendrimers are typically created by segregating the different sides of the chain, with one side drawing electrons and the other donating electrons[12]. Example: Bola amphiphiles

e) **Hybrid Dendrimers**: These dendrimers are composed of carbosilane and aromatic shell. It was developed by Dial's-alder by cycloaddition of pre synthesized carbosilane.

f) Metallo dendrimers: Metallo dendrimers are type of dendrimers which incorporate metal atom. It is prepared by complex arrangement technique which happens either at the fringe surface or in the inside of the particle. These dendrimers also having both electrochemical and glow properties[13].

g) Tectodendrimers: Tectodendrimers are widely used in biomedicine, pharmaceutical and personal care. They are also used for identification of disease cell to diagnosis.[13] Example:Stratus® CS Acute Care™ and Starburst®

h) Multilingual Dendrimers: Multilingual dendrimers having both dendritic and linear characteristics. These are consisting of multiple copies of a specific functional groups. Example: Vivagel

i) Multiple Antigen Peptide Dendrimers: Peptide with Multiple Antigens Dendrimers are dendron-like structures created with polysineskelton.These kinds of dendrimers were shaped and found to have various natural applications for example, in antibody arrangement (vaccine preparation) and for diagnostic purposes[14].

2.2 Dendrimer Classification Based on Property

1) Hydrophilic dendrimers: Most commercially available hydrophilic dendrimers are PAMAM. These dendrimers are prepared by Michael addition reaction which happens in the middle of an alkyl diamine core (ethylenediamine) utilizing monomers of methyl acrylate and that resulted production of branched monomers. These monomers were converted into small particle (OH and-NH) which also reacted with ethanol amide and ethylenediamine respectively to form surface group moieties. On hydrolysis of methyl ester, these anionic dendrimers with four-COOH groups are formed. When the growth of dendrimers reaches a certain critical point, the synthetic yield is reduced due to the stearic factor, which causes overcrowding of branching arms. This technique was reasonable transporters for the drug molecule because of their high-water solubility, large surface group[15].

2) Biodegradable Dendrimers: The goal of developing biodegradable dendrimers was to create large molecular polymers with a high disposition in tissue and rapid elimination via urine. These are formed by the incorporation of ester by enzymatic cleavage. Because of their biodegradability and biocompatibility, dendrimers are used in anticancer and gene therapy[16].

3) Amino acid-based dendrimers: Amino acid-based dendrimers are created by combining blocks with different properties such as hydrophobicity, chirality, optical properties, and so on. Because of their branching units, these dendrimers can also be used as protein mimics and gene drug delivery systems. These dendrimers are typically produced by amino acids or peptides.

4) Glycodendrimers: Glycodendrimers are used as a carrier for cancer therapy as well as an immune stimulant. Carbohydrate interacts with receptors that control a variety of normal and abnormal processes, resulting in the formation of these dendrimers. This interaction results in a powerful multivalent ligand receptor system. Glycodendrimers are used as a cancer therapy carrier as well as an immune stimulant.

5) Asymmetric dendrimers: Bow tie polyester dendrimers are another name for asymmetric dendrimers. Gillies and Fréchet were the first to create it by tying dendrons of a linear core molecule together. The finished structure is made up of orthogonal dendritic architecture. Lee and colleagues also used click chemistry to create G3 asymmetric dendrimers.

6) Hydrophobic Dendrimer: These dendrimers require adequate aqueous solubility for systemic delivery.

III. METHODS FOR SYNTHESIS OF DENDRIMERS

Dendrimers can be synthesised using a variety of methods, including divergent growth, double exponential and mixed growth, convergent growth, and hyper core and branched growth.

3.1 Divergent growth method:

Divergent growth method is one of the promising methods for synthesis of dendrimers (Fig. 3). Tomalia and Newkome was first introduced this method for synthesis of dendrimers, and they named as divergent method because of dendrimers grows around core. In this method, synthesis starts from core of the dendrimers, and which attached with arm of dendrimers by adding building blocks in stepwise manner. Sequential core addition results in 3D dendrimer architecture while simultaneously increasing the number of molecular weights and functional groups. The divergent method is used in a two-way process:

1) In the first step, methyl acrylate is used to make an exhaustive Michael addition to the amine initiator core.

2) Exhaustive admiration for the resulting ethylenediamine esters [17].

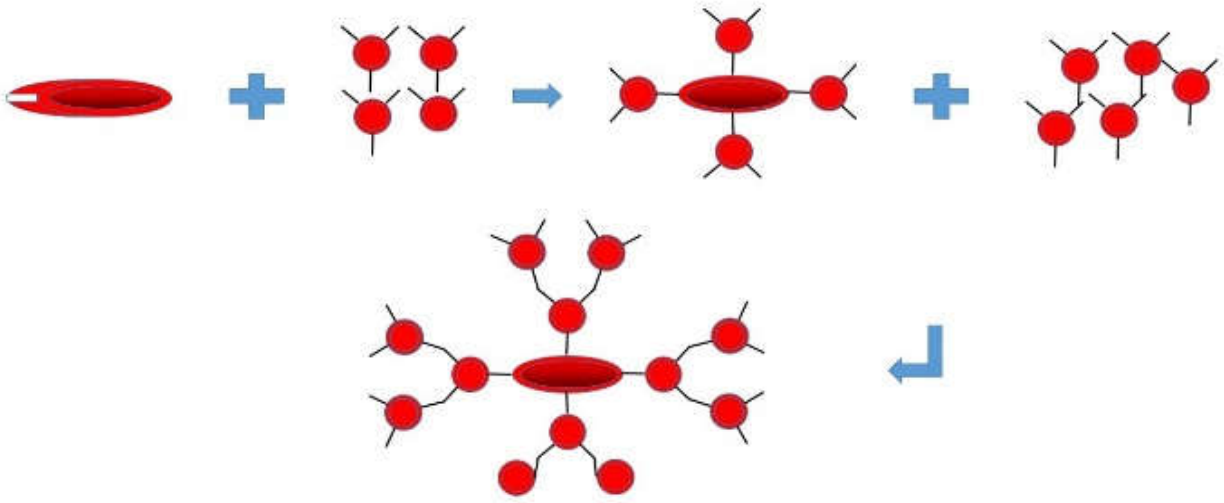

Fig. 3 Divergent method of dendrimer synthesis

3.2 Convergent growth method:

Divergent growth method shows solubility problem. To overcome this problem the method of convergent growth has been developed for the synthesis of dendrimers. In Convergent growth method synthesis starts from exterior and progress towards inward branching unit are grown (Fig.4). When they become large enough, they are connected to the core molecule[18].

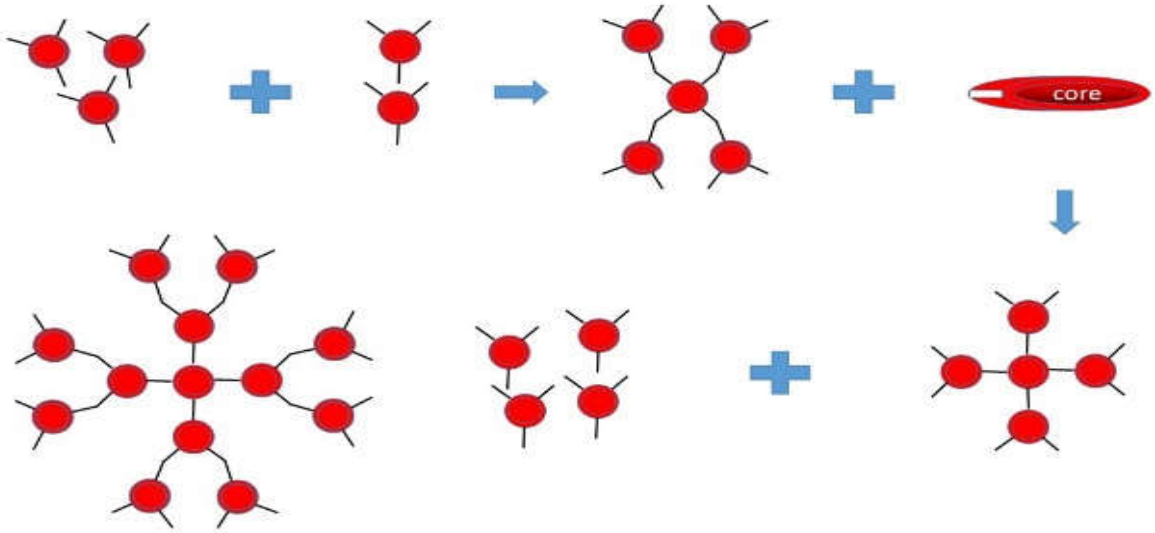

Fig.4 Convergent method of dendrimer synthesis

3.3 Hyper core and branched method:

As comparison to convergent growth method and divergent growth method, hyper core and branched method was widely used for synthesis of higher generation dendrimers because of it required few advanced steps. Repeating unit of oligomers combinedly produced desired structure of dendrimers.

3.4 Double exponential and mixed growth:

Both convergent growth method and Divergent growth method are required for synthesis of dendrimers. It is the most progressed strategy are used to produced triangle that also used in growth process[19].

III. Interaction of anti-cancer drug with dendrimers

Dendrimers are witnessed to deliver the anticancer drugs so as to improve the solubility and reduce the toxicity with precise targeting to cancer cell. Anti-cancer drug is interacted with dendrimers by 3 different distinctive mechanism such as: physical encapsulation, electrostatic interaction, covalent conjugation.

(A) **Physical Encapsulation**: Dendrimer and drug molecule internal cavities can interact through a variety of mechanisms, including physical encapsulation, hydrophobic interaction, and hydrogen bonding. Dendrimers can directly encapsulate foreign molecule into macromolecular interior due to it having spherical shape and internal cavities [20]. Through hydrophobic interaction, internal cavities of

dendrimers are interacted with low water-soluble drug [21]. In internal cavities nitrogen and oxygen are present which interact with drug by the help of hydrogen formation. Because of their well-defined structure, the drug ionic group and opposite charge of dendrimers can interact via hydrophobic interactions, hydrogen bonding, or electrostatic interactions (Fig. 5).

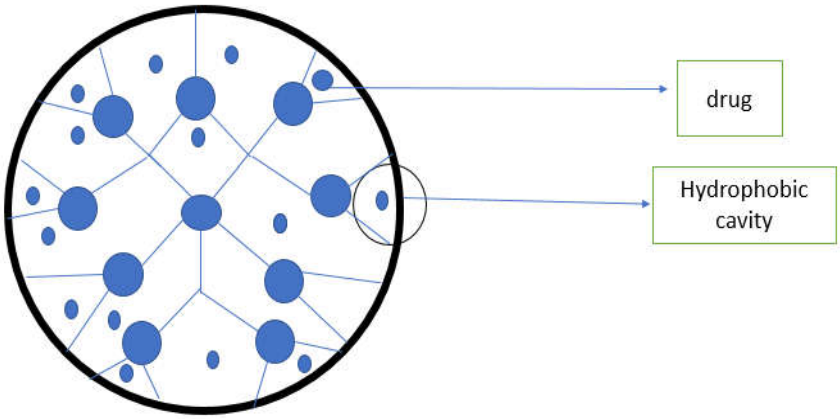

Fig. 5, Drug encapsulation in dendrimers by physical encapsulation

B) Electrostatic interaction: The presence of amine group and carboxyl group in dendrimers having inherent application for improving solubility of hydrophobic drug through electrostatic interaction[22]. Drugs with carboxylic groups, such as ketoprofen, ibuprofen, and naproxen, have complexed with dendrimers via electrostatic interaction. Different ionizable drug complex with multifunctional surface of dendrimers through electrostatic interactions. Because of electrostatic interaction, many medications, including ibuprofen, piroxicam, indomethacin, and benzoic corrosive, have stable complexes [23].

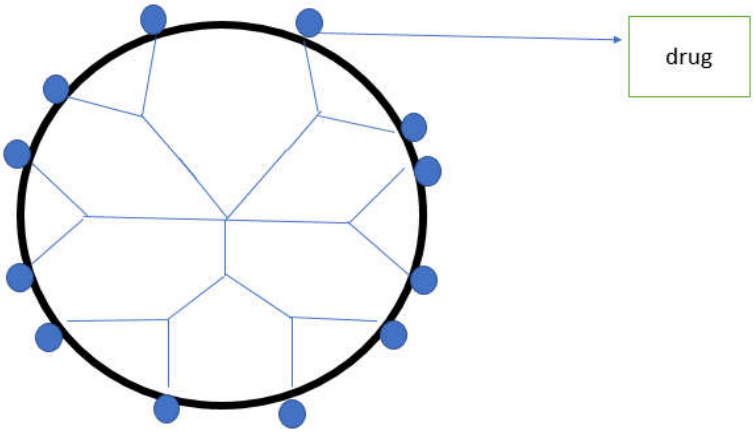

Fig. 6,Chemical conjugation for drug encapsulation in dendrimers.

C) Covalent conjugation: Large no of functional group present in dendrimers help for covalent conjugation of drug with appropriate functional group [24].PEG, p-amino benzoic acid, p-amino hippuric acid, and lauryl chains all help with drug covalent conjugation with dendrimers. This prodrug strategy has been shown to improve drug stability and release kinetics. Many studies have successfully linked PAMAM dendrimers to penicillin V, venlafaxine, 5-aminosalicylic corrosive, naproxen, and propranolol, with the results demonstrating improved drug solubility and release kinetics when compared to standard anti-cancer drugs. Some anticancer drugs, including cisplatin, doxorubicin,

epirubicin, methotrexate, and paclitaxel, have been conjugated with dendrimers and have shown promise in clinical trials (Fig.6).

IV. Dendrimers Application in Cancer Therapy

Traditional drug therapy is most effective way of treatment of cancer. Drug treatment incorporate chemotherapy, hormonal therapy, immunotherapy etc which are used to delivery of drug to a specific cell for destroy cancer cell. Anticancer medications that are hydrophobic, such as paclitaxel (PTX), camptothecin, 5-fluorouracil, methotrexate, and DOX free base, make administration difficult. In recent work has proposed that nanoparticles as dendrimers might be a key stone for future therapy of cancer. The area of oncology could be more effective utilizing dendrimer-based nanotherapeutics[25]. To overcome this problem of drug delivery various nanomaterial are investigated. Over decade of year dendrimers is highly branched polymer is playing an important role in cancer treatment. Malignant growth is a known deadliest disease that requires a judicious treatment, diagnosis, and selective therapy for early recovery. These properties of dendrimers display a reproducible pharmacokinetic behaviour that could ensure biodistribution and efficacy. Dendrimers are hence being taken advantage of as a nanotheranostic platform which incorporate a different class of therapeutic, imaging, and focusing on cancer treatment. SylwiaMichlewska et al. (2018) investigated the interaction of anti-cancer small interfering RNA with ruthenium-containingcabosilane-based metallodendrimers (SiRNA). Fluorescence, transmission electron microscopy, and circular dichroism were used to examine both dendrimers. They concluded that ruthenium dendrimers linked with cancer siRNA can be employed as non-viral vectors for siRNA delivery into cancer cells [26].

Dendrimers are widely used as a vehicle for the delivery of various anticancer medications. Due to its well-defined structure and surface functionality which allowed for encapsulation of multiple entities on the surface for delivery of anti-cancer drug. Jesus et al. (2002) investigated various dendritic architectures as doxorubicin delivery carriers in vitro and in vivo, including a dendritic scaffold based on 2, 2-bis (hydroxymethyl) propanoic acid. Both invitro and in vivo system are water soluble and nontoxic, addition of anticancer drug doxorubicin which resulted that drug release is more rapid. Nonetheless, in vivo biodistribution tests revealed that the DOX dendrimer form accumulated minimally in key organs such as the liver and heart, which increased doxorubicin half-life when compared to free drug [27]. Huang S et.al (2016) synthesized peptide dendrimers for treatment of chemotherapy. They coadministration dendrimer and doxorubicin into PDAC tumour xenograft bearing mice. Both doxorubicin and gemcitabine drug were administered individually into PDAC tumour xenograft bearing mice., a significant improvement will beobserved. They concluded that combined treatment of dendrimers and gemcitabineresulting tumour weight decrease as compared to the treatment with gemcitabine alone [28]. Bartusik-Aebisher D et al (2021) investigated a trastuzumab-dendrimers-fluorine drug delivery system by synthesising and characterising a series of fluorinated dendrimers. They used HPLC, LC, and MS techniques to characterise the samples.They came to the conclusion that the trastuzumab-dendrimer-fluorine drug delivery system is more effective in the treatment of breast cancer than trastuzumab alone [29]. Ngan le et al. (2016) investigated a thermo-sensitive 5-fluoro uracil-loaded carboxylic poly (N-isopropylacrylamide) polymer grafted G3 PAMAM dendrimer (PAMAM G3.0-PNIPAM) as an effective high drug loading carrier against breast cancer. The cytotoxicity activity of a 5-FU loaded PAMAM G3.0-PNIPAM nanogel on MCF-7 breast cancer cells was assessed using a sulforhodamine B colorimetric assay. The results showed that the PAMAM G3.0-PNIPAM nanocarrier had effective antiproliferative activity on MCF-7 breast cancer cells, indicating that the nanocarrier has a high potential for 5-fluorouracil delivery[30].

Another study of dendrimers used in cancer therapy Kellyet.al (2018) synthesized pH Low Insertion Peptide (pHLIP)-dendrimers-DOX (doxorubicin) conjugate for cytosolic delivery of the cancer chemotherapeutic.in this method both dendrimers and single DOX conjugate inserted into membrane bilayer which resulted that single DOX conjugate will help translocation of membrane in faster rate[31].

In recent investigation Nigam et al. Developed generation 2 (g2) PAMAM dendrimers from modification iron oxide which loaded with doxorubicin for treatment of cervical cancer of HeLa cancer cells by using both chemotherapy and magnetic therapy. Combination treatment reduce cancer cell viability[32]. Yousef et al. developed a platform for HCC targeted drug delivery using nanoscale G4 PAMAM dendrimers loaded with a potent anticancer curcumin derivative (CDF). They characterized cytotoxicity assay in HCC cell line by using in vivo xenograft model which show CDFnb was more potent as compared to neoplastic drug such as Doxorubicin, Sorafenib and Cisplatin[33].

Table.1. Dendrimers Application in Cancer Therapy

Polymer/dendrimers name	Drug	Cellline/application	Result
Peptide dendrimers [34]	Doxorubicin	Pancreatic cancer	Dendrimers helps free drug accumulation in tumour tissue.
Flurinated dendrimers [35]	Trastuzumab	Breast cancer	In 3D breast cell culture, the efficacy of the trastuzumab-dendrimer-fluorine drug delivery system can be assessed at 1.5 T.
PANAMA dendrimers [36]	-	Breast cancer	According to our findings, PAMAMs may have important therapeutic effects against HER2-positive breast cancer through the JNK1/2/3, ERK1/2, and HER1/2 signalling pathways.

PANAMA G3 dendrimer [37]	celecoxib and/or Fmoc-L-Leucine	Cancer treatment/human cell line	Biotinylated G3 PAMAM dendrimers in combination with the COX-2 inhibitor celecoxib and the PPAR agonist Fmoc-L-Leucine (1:1) appear to be a promising candidate for local therapy of glioblastoma but not skin cancer.
PAMAM dendrimers [38]	Methotrexate	Breast cancer / Cancer cells MDA-MB-231	The cytotoxic effect of OS-PAMAM conjugate is enhanced by glycosylation in MDA-MB-231.
PAMAM dendrimers generation (G) 4.0, 5.0 and 6.0 [39]	Magnetic nano particle	Liver cancer cell	In vitro studies revealed that using dual therapy resulted in the desired cell death mechanism-apoptosis.
Peptides Dendrimers [40]	Dox (doxorubicin)	3d multicellular PDAC	Combination treatment of multi functionalities of dendrimers promoting free drug accumulation and better result than individual drug.
PAMAM dendrimers [41]	Methotrexate	KB cells/ Cancer therapy	As a result, the polyvalent MTX on the dendrimer serves as a targeting molecule as well as a chemotherapeutic drug. The newly synthesised G5-MTXn conjugate has the potential to be used in cancer therapy as a FR-targeted chemotherapeutic.
PANAMA dendrimers [42]	dox	Ca9-22 human gingival cancer cell line/cancer therapy	Both PCI strategies were ineffective in increasing the cytotoxicity of PAMAM-amide-DOX conjugates.
Peptide dendrimer [43]	dox	Ovarian cancer therapy using SKOV-3 and COS-7 cells	As a result, the mPEGylated peptide dendrimer-DOX conjugate-based nanoparticle may be a promising candidate for ovarian cancer therapy as a nanoscale and enzyme-sensitive drug delivery vehicle.

V. Future prospective

The principal objective of nanomedicine is to deliver suitable substance for diagnosis of disease dendrimers based nano medicine will help delivery of drug and through understanding the biological process.[44]Dendrimer drug administration via various routes, such as oral, nasal, transdermal, and parental, has recently shown promising results. They are also found to be more focused on gene delivery, boron neutron catch treatment, and MRI contrast agent. Improved synthesis technique and knowledge of dendrimer properties. Dendrimers will be a promising vector for the development of new drugs and medical applications. The tumour has an acidic pH (5-6) while the pH of the body's circulation is neutral (7.4). This consideration will be critical in the development of next-generation dendrimers nanocarriers. By using imaging probes such as fluorescent dye and radio nuclei it will be effectively used for discovery of cancer growth cells. In latest investigation of dendrimers, the majority of the research work was completed with PAMAM dendrimer while other dendrimers can be investigated soon[45].

VI. Conclusion

The cancer therapy is one of the greatest exploring subjects of the decade years because of its complex recognition and determination. Advanced chemotherapy cause side-effect by affecting healthy cells to avoid these side effect, dendrimers based nanocarrier is one of the best treatments for cure cancer cell.Several companies, including Dendritech (Midland, Michigan) and nano synthons, have created high-quality dendrimers (PAMAM dendrimers) for basic research and translational studies. In large scale, dendrimers are served as reliable source for building block of nanomedicine. Nowadays, producing dendrimers with uniform drug and ligand loading is a difficult task[46].The use of nanoparticles in biomedicine has seen rapid growth in recent years, but knowledge about the safety of nano carriers is lacking. A new drug delivery system is being tested in clinical trials to determine the side effects of nano carriers. Animal study has been carried out to identify risks related to nano particle use, elimination process [47]. Because of their surface modification and ability to interact with charged functional groups, dendrimers are important tools for drug discovery. Traditional chemotherapeutic methods have been used to boost the effectiveness of anticancer drugs delivery into tumours. These strategies based on used of nanoparticle loaded drug for clinical and pre-clinical study. Dendrimer serve as a vehicle for the conjugation or encapsulation of drugs before delivery to tumours. PAMAM, PPI, and PLL dendrimers are primarily used for this distribution to the tumour location through passive or active targeting. Numerous advancements in the development of safe and effective dendrimer-based formulations have been made in order to increase the specificity and effectiveness for the detection and treatment of cancer.Dendrimers' utility in fields as in synthesis, drug transport, biotechnology, nanotechnology, detection, catalysts, and cosmetics will determine how widely they are used in research in the future. Dendrimers act as drug carriers by encapsulating and conjugating drugs to tumour cells via PAMAM, PPI, and PPL via active or passive targeting.Many advanced dendrimers have been developed for the preparation of safe and effective formulations for cancer diagnosis. The future extent of dendrimers in research relies upon in such area that is synthesis, drug delivery, nanotechnology, detection, cosmetic etc.

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