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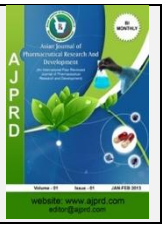

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Review Article

Recent Advancement In Nanocarrier Systems For Cancer Targeting

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A B S T R A C T

Cancer is a disease that has a complicated pathological process. Current chemotherapy has issues such as lack of selectivity, cytotoxicity, generation of multi-drug resistance, and the formation of stem-like cells. The novel treatment modalities enabled by nanomaterial characteristics have expanded their reach in cancer therapy beyond traditional medication delivery. Nanotechnology has been actively researched and used in cancer treatment because nanoparticles can serve as an effective medication delivery mechanism. Nanoparticle-based drug delivery provides distinct benefits over traditional drug administration, including greater stability and biocompatibility, increased permeability and retention effect, and precision targeting. There are numerous major categories of nanomaterials utilized in cancer treatment. These nanomaterials, which target cancer cells, the tumor microenvironment, and the immune system, have been modified for a variety of cancer treatments in order to overcome toxicity and lack of selectivity, as well as to improve drug capacity and bioavailability. Furthermore, nanoparticle-based drug delivery systems have been found to help overcome cancer-related treatment resistance. In cancer therapy, nanoparticles can be used to encapsulate active pharmacological substances and deliver them to the tumor location more efficiently. This overview lists the several types of nanoparticles that have been tested in clinical trials for cancer therapy. Furthermore, the most recent advancements in the use of nanoparticles in cancer therapy are emphasized.The literature for this study was compiled using databases such as PubMed, Google Scholar, and ScienceDirect on nanoparticles in the treatment of cancer have been collected. The present article focuses on nanotechnology advancements, specifically nanocarriers for anticancer medication delivery. It covers nanoparticles, polymeric micelles, dendrimers, hydrogels system and finally the future prospects of the nanocarrier.

KEYWORD: Nanocarrier, Anticancer, Nanoparticles, Nanomedicines

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INTRODUCTION:

Cancer-related cases and death are increasing rapidly globally. The causes are complicated, but they reflect population aging and expansion, as well as changes in the incidence and distribution of cancer risk factors, some of which are connected with socioeconomic development. [1] Cancer is intimidating in its breadth and depth of variation, covering genetics, cell and tissue biology, pathology, and response to therapy. An avalanche of "big data" regarding the numerous symptoms of cancer-related disorders is being generated by ever more sophisticated experimental and computational instruments and technologies. [2] Cancer develops when the immune system fails to function correctly and/or when the number of cells produced is too large for the immune system to destroy. Under some situations, such as an unfavorable environment (due to radiation, pollutants, etc.), a bad diet (unhealthy cell environment), persons with hereditary predispositions to mutations, and people of senior age, the rate of DNA and RNA mutations might be excessive. [3] Failures in medical diagnosis and therapy may result in an increase in advanced stages illness and death. [4] The choice of mortality as the primary indicator of cancer progress, rather than incidence or survival, concentrates emphasis on the result that is most consistently recorded and of most public concern: death. [5] Though chemotherapy is effective in certain cases, the primary negatives are the restricted accessibility of medications to tumor cells, which necessitates high dosages, their unacceptable toxicity, the development of multiple drug resistances, and their non-specific targeting. [6] Non-specific interactions of soluble immunotherapeutic payloads with immune cells, nucleases, and proteases not only diminish

immunostimulatory responses but also lead to immunological-related side effects. As a result, there is an urgent need to create effective delivery systems for transporting therapeutic/immunological payloads to their target cells and/or tissues while exposing them to as little as possible of their biological milieu and minimizing side effects. [7] As anti-tumor medications are not site-specific and hence produce non-specific cytotoxic activity over healthy cells in the bone marrow, gastrointestinal epithelia, and hair follicles, the underlying processes for the genesis of side effects and toxicities. [8]

Targeted drug delivery is a means of administering medication to a patient in such a way that the concentration of the medication in some sections of the body is higher than in others. The goal of targeted drug delivery is to concentrate the medicine in the tissues of interest while decreasing the relative concentration of the medication in the other tissues. [9] A carrier for a specific cellular target is conjugated with the medication in this technique to generate a prodrug that is less toxic than the parent drug. The carrier serves two purposes. The first is to lower the drug's toxicity to normal cells, and the second is to increase the drug's selectivity for selected cells. When the prodrug reaches the target cell, it is converted from an inactive (or less toxic) form to an active form that performs its physiological activities. [10] The medication delivery mechanism needs to be targeted, either passively or specifically, in order to ensure high and specific accumulation at the infected location while avoiding healthy organs and tissues. Finally, the drug must be released at the infected spot to have a targeted therapeutic impact. [11] TDDSs are frequently used in tumor treatment and bioimaging. Liposomes, mesoporous silica nanoparticles, gold nanoparticles, iron nanoparticles, polymers, micelles, and dendrimers are all types of nanoparticles. These nanocarriers are being widely researched for use in the development of TDDSs for tumor treatment. [12] Despite the fact that numerous therapeutic modalities, including as immuno, photothermal, photodynamic, gene, and hormone therapy, show remarkable cancer-eradicating potential in preclinical research, surgery, radiation, and chemotherapy remain the first-line treatment options for most tumors. [13] Because of their significance in shielding therapeutic drugs from degradation, permitting effective drug concentration in target cells or tissues, overcoming drug resistance, and their comparatively tiny size, nanocarriers have been preferentially employed in breast cancer chemotherapy. [14] Clinical translation is hampered by factors other than species differences. Patient heterogeneity can potentially hinder the efficacy of nanomedicines, and there is currently little study on the interplay between nanomedicines and in stratified patient groups. As a result, few nanomedicines are suggested as first-line therapy alternatives, and many demonstrate benefits in just a tiny proportion of patients. [15]

Nanocarrier has the potential to solve these issues. [17] Nanocarriers are colloidal drug carrier systems with submicron particle sizes of 500 nm or less. Nanocarriers have been actively researched in recent decades due to their enormous promise in the field of medicine delivery. Nanocarriers have the power to change the fundamental characteristics and bioactivity of medications due to their high surface area to volume ratio. Furthermore, nanocarrier physiochemical properties can be tuned by varying their compositions (organic, inorganic, or hybrid), sizes (small or large), shapes (sphere, rod, or cube), and surface properties (surface charge, functional groups, PEGylation or other coating, and attachment of targeting moieties). [16]On their way to their destination, nanocarriers meet several hurdles, including mucosal barriers and non-specific absorption. To address the issues of tumor targeting using nanotechnology, it is vital that we integrate the rational development of nanocarriers with a fundamental understanding of the biology of tumors. [17]

The development of multidrug resistance against chemotherapeutic drugs is the most significant barrier in the clinical therapy of cancer. To overcome the limits of chemotherapy, researchers have been creating technical innovations that will allow for considerable progress in oncology by allowing the administration of chemotherapeutic drugs with greater drug content levels to the targeted sites. Several nano-drug delivery systems intended for tumor-targeting have been studied in preclinical and clinical studies, with encouraging results in the clinical treatment of malignant tumors.The present article focuses on nanotechnology advancements, specifically nanocarriers for anticancer medication delivery. It also covers polymeric nanoparticles, micelles, dendrimers, hydrogels, and other nanocarriers. Finally, existing issues and future prospects have been discussed. [18]

NANOPARTICLES: -

Over the past few decades, nanotechnology has been used more and more in medicine, particularly in applications for safer and more efficient tumor targeting, therapy, and diagnostics.

Many advantages of nanoparticle (NP)-based drug delivery systems in cancer treatment have been demonstrated, including excellent pharmacokinetics, specific targeting of tumor cells, reduced side effects, and drug resistance. [19] The function of nanoparticles as immunogenic cargo in standard radio- and chemotherapies, as well as advanced adjuvant treatment, is also being studied. The biocompatibility of nanoparticles aided in the development of novel nanostructures, which are presently serving in completely unexpected functions (as artificial antigen-presenting cells (aAPCs) or as in vivo repository of immunostimulatory chemicals) for long-term anticancer action. [20] Polymeric nanoparticles are often formed through spontaneous complex self-assembly, with medicinal chemicals encapsulated within the PNP core. PNP surface properties can be modified by utilizing different polymer end-groups or by connecting specific polymers to the developed PNPs. PNPs can manage several cancer medicines that have significant cytotoxicity by releasing modest dosages over time. Antibodies, peptides, or small-molecule targeting ligands can also be attached on PNP surfaces in order to speed up and allow targeted interactions with cellular receptors or tissue components. PNPs can transport not only traditional medications, but also proteins, nucleic acids, and diagnostic chemicals. [21] Nanoparticles can be created chemically or organically.Many negative

consequences have been linked to chemical synthesis procedures due to the presence of harmful chemicals absorbed on the surface. [22] Nanoparticle preparation methods are a significant aspect of this problem. They enable the creation of polymer nanoparticles with appropriate characteristics for medication delivery and targeting. Polymer nanoparticles with a wide range of characteristics may now be synthesized under controlled circumstances thanks to advances in polymer chemistry and polymer colloid physico-chemistry. [23] There are several types shown in the table (1) of nanoparticles that are uses as a nanomedicine for the treatment of cancer.

Table 1: Different types of nanoparticles and its properties

Types	Properties
Liposomes	Spherical lipid vesicles (typically 50-500 nm in particle size) formed by emulsifying natural or synthetic lipids in an aqueous media and consisting of one or more lipid bilayers. [26]
Niosomes	cholesterol, nonionic surfactant (alkyl or dialkyl polyglycerol ethers), and charge-inducing substance combine to produce tiny lamellar molecules.
Dentrimers	well defined artificial macromolecules characterized by a large number of functional groups and a tight molecular structure. [43]
Polymeric Micelles	PEG-based amphiphilic block copolymer micelle carriers encased in poly[ethylene glycol]-poly[gamma-benzyl-l-glutamate] (PEG-PBLG) micelles produce nanoscopic core/shell structures.[50],
Hydrogel System	Hydrogels are three-dimensional networks of polymer chains that are cross-linked via either physical or chemical bonds.

METHOD OF PREPARATION:

Nano-Precipitation, Solvent evaporation, salting out, solvent diffusion, hydrothermal and solvothermal syntheses, microwave-assisted processes, polyol method, template-directed synthesis, ionic-liquid assisted methods and other nanofabrication methods have been reported in the literature. The most commonly used fabrication processes are discussed in depth, with references to relevant literature. A thorough examination of their use and shortcomings, with specific emphasis on laboratory scale synthesis, has also been conducted. [24]

Solvent Evaporation - One of the most prevalent ways for preparing polymeric nanoparticles, especially drug-loaded polymeric systems, for pharmaceutical formulations is solvent evaporation. The polymer is typically dissolved in a volatile organic solvent into which the medication is dissolved. The resulting solution is then mixed with the surfactant-containing aqueous phase to produce an emulsion. After the formation of a stable emulsion, the organic solvent is removed, causing nanodroplet dispersion, either by stirring continuously or by increasing the temperature while decreasing pressure. This process was also used to create core-shell particles, which were created by generating and stabilizing the core in organic solvent in the first phase of an emulsion made of water and oil and then dispersing the final aqueous phase with surfactant.[25]

Nano-Precipitation - Nanoprecipitation is the precipitation of a preformed polymer from an organic solution, as well as the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. This nanoprecipitation approach employs a somewhat water-miscible solvent that has been extensively saturated in water to assure the initial thermodynamic equilibrium of both liquids. (26) The approach produces nanoparticles instantly, is a simple process that can be scaled up, and is a one-step operation. The approach needs the addition of two miscible liquids and results in the spontaneous production of nanoparticles during phase separation. Ideally, the first solvent (solvent) is the one in which the polymer and drug dissolve but not the second system (non-solvent). (27) In this process, solvent and nonsolvent phases must be prepared before adding one phase to another with moderate magnetic stirring. Organic solvent evaporation at room temperature or with a rotavapor results in nanoparticles (NPs) suspension in water. Ultracentrifugation and freeze drying are two procedures that might be used in the following stage to remove the aqueous phase. A film-forming substance, one or more drug molecules, a lipophilic surfactant, and one or more organic solvents compose the solvent phase. Organic and aqueous phases are commonly used to distinguish between solvent and nonsolvent phases. (28)

Salting Out - A modified version of the emulsion process known as "salting out" removes the need for organic solvents that are bad for the environment and people's health, such surfactants and chlorinated solvents. To summarize, the drug and polymer are dissolved in an organic solvent that is miscible with water, and the resulting solution is added to an aqueous solution containing the salting out agent and stabilizer while being constantly stirred. This salting out agent hinders organic solvent miscibility in aqueous phase, resulting in the formation of emulsion. A reverse salting out action caused by dilution of the emulsion with an excess of water results in polymer precipitation, which wraps the medication in the polymer matrix and results in the production of nanoparticles.To remove the leftover solvent and salting out agents, the cross flow filtering process is applied. (29)

Solvent diffusion - This is a variation on the solvent evaporation method. Water-miscible solvents such as acetone

or methanol are employed as the organic phase I in this procedure, whereas water immiscible solvents are used as the organic phase II. The production of nanoparticles is caused by the interfacial turbulence induced when these two phases are combined. Despite the fact that this approach creates substantially smaller particles, there are certain drawbacks, such as the existence of leftover organic solvent. (30)

LIPOSOMES: -

Liposomes are self-assembled entities that exist naturally but may also be manufactured in the laboratory. They are made up of one or more lipid bilayers that enclose aqueous compartments and can range in size from tens of nanometers to tens of microns. They may be created from a wide range of lipid ingredients, resulting in a wide range of physical characteristics that can be manipulated. [31] Liposomes are mostly made up of phospholipids, which are amphiphilic molecules with a hydrophilic head and two polar hydrophobic chains. Because of their amphipathic character, phospholipids have a strong inclination to form membranes when distributed in aqueous solutions. They can entrap both lipophilic and hydrophilic substances in the lipid membrane and the watery core, respectively. [32] Liposomes are divided into four types based on their size and number of bilayers: small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), multilamellar vesicles (MLV), and multivesicular vesicles (MVV). Liposomes can be classified as multilamellar with an onion-like structure or unilamellar with a monophospholipid bilayer. As multiple unilamellar vesicles are formed within bigger liposomes, MVV create a multilamellar configuration with concentric phospholipid spheres. [33] The size range is a balance between liposome loading efficiency (which rises with increasing size), liposome stability (which declines with increasing size above an acceptable 80-200 nm range), and extravasation ability (which decreases with increasing size). The membrane has a thickness of around 4 nm and can have a polymer covering and/or ligands with specialized functionalities, such as specific binding or fusogenic activity. [34] Despite massive research and development efforts on liposomes, only a few liposomal products have been authorized for human use thus far. This might be due to a variety of factors, including the toxicity of some liposomal formulations, poor entrapment of molecules and chemicals into liposomes, the instability of the liposomal carriers, and the high expense of liposome manufacture, particularly on large quantities. [35] The advantages and disadvantages of liposome drug carriers are heavily dependent on liposome interactions with cells and their destiny in vivo following injection. In vitro and in vivo investigations of liposome interactions with cells have revealed that either simple adsorption or subsequent endocytosis is the major interaction. Fusion with cell membranes is far less common. The interchange of bilayer ingredients such as lipids, cholesterol, and membrane bound compounds with cell membrane components is the fourth potential contact. [36] For more than 20 years, liposomes have been thoroughly investigated as carriers for the enhanced delivery of a broad range of agents, including lipids, genetic material, immunomodulators, hemoglobin, chelating chemicals, antigens, and chemotherapeutic drugs. [37]The structure of liposomes is shown in the figure (1) that is use for the treatment of cancer.

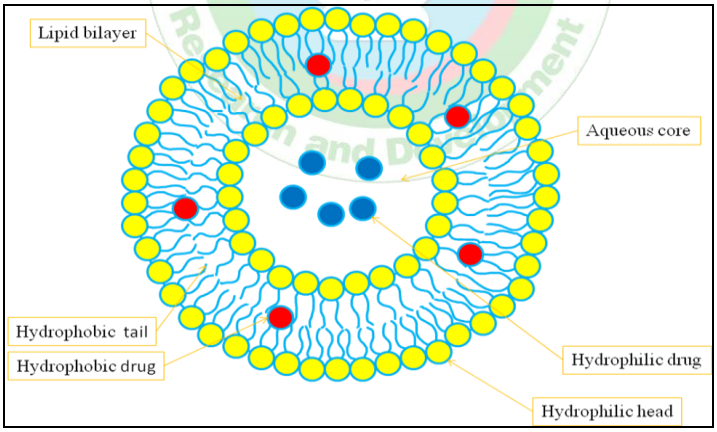

Figure 1: Structure of liposomes with labeling

Here are some of the recent pre-clinical studies or ongoing investigation on liposomes that are used for the treatment of the cancer given the table (2):

Table 2: Some clinical studies on liposomes for the treatment of cancer

Names	Drugs	Diseases	References
FRα-targeted liposomes	matrix protein pDNA	Ovarian cancer	84
HA lipoplexes	CD44 siRNA	Lung cancer	85
2X3-DOPE/FC liposomes	MDR1 siRNA	Squamous carcinoma	86
HA-P-LP	shRNA mRIP3-pDNA	Colon cancer	87
pegSA lipoplexes	BMP-9 pDNA	Osteoporosis	88

T7-LPC	EGFR siRNA	Glioma	89
Liposome-siRNA nanocomplex	STAT3 siRNA, curcumin	Skin cancer	90

NIOSOMES:

Niosomes, or NSVs, are non-ionic surfactant-prepared vesicles. In terms of structure and physical features, niosomes are comparable to liposomes. They are created as unilamellar or multilamellar vesicles using the same techniques and under the same circumstances. [38] Niosomes are made up of two sorts of components: nonionic surfactants and additions. The vesicular layer is formed by non-ionic surfactants, and the additions utilized in niosome production include cholesterol and charged molecules.[39] The hydrophobic portions of the molecule are orientated away from the aqueous solvent in this closed bilayer form, whilst the hydrophilic head is in contact with the aqueous solvent. It is similar to phospholipid vesicles in liposomes and hence allows for the trapping of hydrophilic medicines. Nonionic surfactants have been exploited as alternatives to phospholipids due to their low cost, stability, and simplicity of storage. [40] Mechanical or thermal energy is frequently required for the construction of closed bilayers. Niosomes are classified into three types based on their size and bilayer structure. Small unilamellar vesicles (SUV) (10-100 nm), large unilamellar vesicles (LUV) (100-3000 nm), and multilamellar vesicles (MLV) with several bilayers. [41] Various procedures are used to manufacture niosomes for medication administration and gene therapy vectors. Furthermore, for specialized purposes, they might be coated with various types of agents such as polyethylene glycol (PEG), hyaluronic acid (HA), antibodies, and so on to improve targeting, increase circulation, and target obtaining time. [42] Some of these surfactants, such as Span and Brij, are already used as pharmaceutical excipients. [43] Niosomes have been intensively explored in recent years for their potential to function as a carrier for the transport of medicines, antigens, hormones, and other bioactive molecules. Aside from that, niosomes have been employed to tackle medication insolubility, instability, and fast degradation. [39]Niosomes are regarded to be better options for administration of drugs than liposomes because to considerations such as cost, stability, and furthermore. Using niosomes, many drug delivery methods such as targeted, ocular, topical, parentral, and many more are achievable. Niosomes are a viable drug delivery vehicle because they are non-ionic; they are less toxic and increase the therapeutic index of drugs by confining their activity to target cells. [44] The use of vesicular (lipid vesicles and nonionic surfactant vesicles) systems in cosmetics and for therapeutic response may provide several benefits, including higher patient compliance in comparison to oily dosage forms, the ability to act as a depot and release the drug in a controlled manner, and the ability to accommodate drug molecules with a wide range of solubilities. [45]The structure of niosomes is shown in the figure (2) that is use for the treatment of cancer.

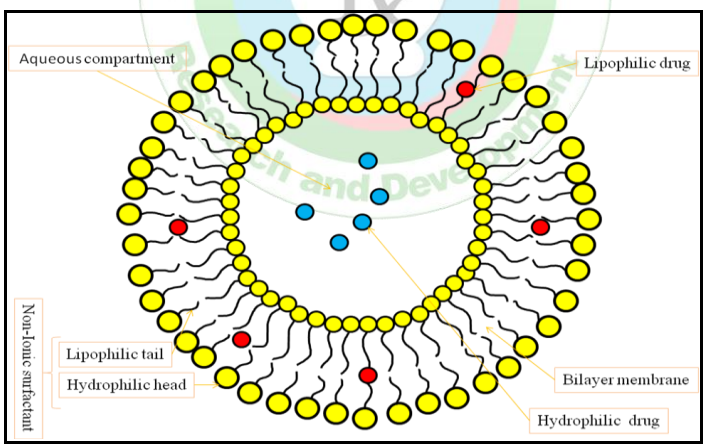

Figure 2: Structure of Niosomes with labeling

Here are some of the recent pre-clinical studies or ongoing investigation on niosomes that are used for the treatment of the cancer given the table (3):

Table 3: Some clinical studies on niosomes for the treatment of cancer

Names	Drugs	Diseases	References
Melittin-loaded niosomes	Melittin	Breast cancer	91
Two Anticancer Drugs Models	Oxaliplatin, Paclitaxel	Colorectal cancer	92
Gold nanoparticles loaded into niosomes	*Artemisia annua* extract	Ovarian cancer	93
e3O4@PLGA-PEG@FA niosomes	Folic acid (FA), curcumin (Cur)	Cervical cancer	94
Doxycycline-loaded niosomal	Doxycycline	Prostate cancer	95

Paclitaxel-loaded niosomes	Paclitaxel	Breast cancer	96
Tamoxifen-Loaded Niosomes	Tamoxifen	Breast Cancer	97

DENTRIMERS:

The word "dendrimer" (Greek: dendron=tree, meros=part) defines the architecture of this new form of molecule in terms of appearance. Although the older word "cascade molecule" is more appropriate for designing their own nomenclature, the term "dendrimers" has now become entrenched. [46] Dendrimers are massively branched polymeric polymers made up of three distinct architectural constituents: core, branches, and terminal functional groups. The core, which can be an atom or a molecule with at least two identical chemical functional groups, is the center portion of the dendrimeric scaffold. [47] It has a well-defined core-shell architecture and a limited polydispersity due to the specific synthesis method. The synthetic technique might additionally adjust dendrimer size, surface charge, peripheral functional groups, and solubility. Higher-generation dendrimers, for example, have a greater size, a larger inner cavity, and more terminal functional groups. [48] Dendrimers fall in between molecular and polymer chemistry. They belong to the molecular chemistry world because of their step-by-step regulated synthesis, and they belong to the polymer world because of their repeated monomer structure. [49] Dendrimers have found widespread use in supramolecular chemistry, most notably in host-guest interactions and self-assembly processes. Dendrimers have unique properties that make them intriguing candidates for a variety of applications. Dendrimers are highly defined artificial macromolecules distinguished by a large number of functional groups and a compact molecular structure. [50] The dendritic surface's high density of exo-presented surface functions makes it well-suited as a nano-scaffold when close proximity of functional groups is critical (polyvalency) or for receptor-mediated targeting. The interior, on the other hand, is ideal for host-guest interaction and encapsulation of guest molecules. [51] Dendrimers' characteristics differ from those of ordinary polymers. Dendrimers are employed in nanomedicine research because of their small size. They have been shown to be beneficial as drug delivery or carrier systems for pharmaceuticals and genes, but research have revealed that several dendrimers have medical applications of their own, owing to their antifungal, antibacterial, and cytotoxic qualities. [52] Dendrimer-mediated drug delivery research has primarily focused on the delivery of DNA drugs (genes or gene inhibitors) into the cell nucleus for gene or anti-sense therapy, with numerous reports published on the potential use of unmodified amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing DNA transfection into the cell nucleus. The exact structure of these host-guest binding motifs has not been determined in detail, but it is presumably based on acid-base interactions between the anionic phosphate moieties in the DNA backbone and the positively charged primary and tertiary amines in the dendrimer. [53]Dendrimers are more likely than other polymers to fulfill the stringent regulatory standards for polymer-based products designed for human use due to their unique and precise molecular makeup. Furthermore, the biocompatibility and toxicity of dendrimers may be controlled during synthesis, particularly by the careful selection of functional groups at the perimeter. [54] Many additional areas of biological chemistry may benefit from the use of dendrimer systems. Some of the numerous areas of exciting active dendrimer research that are outside the scope of this article include very sensitive analytical devices, MRI contrast agents, prion research, burn therapy, and EPR imaging with spin-labeled dendrimers. [55]

Here are some of the recent pre-clinical studies or ongoing investigation on aptamers based dentrimers that are used for the treatment of the cancer given the table (4):

Table 4: Some clinical studies on aptamers and genes based dentrimers for cancer

Aptamers	Genes	Diseases	References
AS1411	shRNA plasmid	Lung cancer	98
EpDT3	LncRNAsMEG3	Prostate cancer	99
S6 aptamer	MiR34a	Lung cancer	100
GA)7 extended A9 aptamer primer-CCAAGGCCTG	Unmethylated CpG	Prostate cancer	101
miRNA		Breast cancer	102

POLYMERIC MICELLES:

Polymeric micelles have sparked considerable attention in recent years as innovative colloidal delivery methods capable of meeting the requirements of an ideal and adaptable drug carrier. [56]Polymeric micelles are amphiphilic block copolymer-based nanoscopic core/shell structures. Polymeric micelles are particularly well suited for drug administration due to their inherent and adjustable characteristics. [57] The growing interest in the use of polymeric micelles for therapeutic targeting is primarily due to their nanoscopic size and segregated core/shell design. [58] The polymeric micelle core serves as a reservoir for hydrophobic bioactives, while the shell offers colloidal stability. The shell, in conjunction with the tiny size of polymeric micelles, plays a crucial function in inhibiting opsonization, protein adsorption, and increased penetration and retention effect (EPR) when

accumulated in tissues with leaky vasculature. [59] Amphiphilic block copolymers having a hydrophilic and a hydrophobic block are first shown to create such different domains in a micelle structure by spontaneous self assembly as a result of hydrophobic interactions in aqueous solutions. [60] In water, block copolymers self-assemble form spherical micelles. A polymeric micelle is typically composed of hundreds of block copolymers and has a diameter of 20-50 nm. [61] The inner core of polymeric micelles is the hydrophobic part of the block copolymer, which encapsulates the poorly water-soluble drug, whereas the outer shell or corona of the copolymer's hydrophilic block protects the drug from the aqueous environment and stabilizes the PMs. [62] When the core-forming segments are held constant, increasing the length of the hydrophilic chains of the corona will result in an increase in the value of the CMC. [63] Individual surfactant molecules within the hydrophobic core of polymeric micelles are covalently linked. This connection precludes dynamic monomer exchange between free solution and micellar pseudo-phase. This gives the polymeric micelles stiffness and stability. [64]Micelle formation is caused by two factors. One is an attractive force that causes molecules to bind together, while the other is a repulsive force that prevents micelles from growing indefinitely to a separate macroscopic phase. When dissolved in a solvent that can be selective for either the hydrophilic or hydrophobic polymer, amphiphilic copolymers self-associate. [65] The drug-polymer bond can be designed to dissolve under specified conditions, allowing the medication to be released. Polymeric micelles encapsulate the active metabolite of the extensively utilized in this manner. [66] Polymeric micelles' uses are connected to their distinctive core-shell design, which provides a place for the encapsulation of hydrophobic medicines, protein, or DNA via physical or chemical binding mechanisms. [67] Polymeric micelles have shown special use in the administration of cancer therapies based on physiological changes associated with the tumor, such as increased permeability and retention and the improved permeability and retention hypothesis. [68] As previously stated, micelles are created utilizing amphiphilic polymers that self-assemble to form vesicles with nanometre diameters. The micelles extravasate via the weakened endothelial cell junction and eventually aggregate in the tumor microenvironment due to their nano-size. Polymeric micelles are swallowed more effectively than other nano-sized vesicles such as liposomes and solid lipid nanoparticles because extravasation is size-dependent. [69] Furthermore, when compared to more contemporary nano-DDSs such as liposomes, nanoparticles, and dendrimers, PM has a better drug loading capacity as well as increased stability. PM has attracted increased scientific attention as an effective medication carrier in recent years due to its promising characteristics. [70] Many people are interested in using polymer micelles as nanocarriers for physiologically active substances like medicines. Polymer micelles that are susceptible to environmental changes, such as pH and temperature, or that may be disturbed by external stimuli are ideal in this respect. [71]The structure of polymeric micelles is shown in the figure (3) that is use for the treatment of cancer

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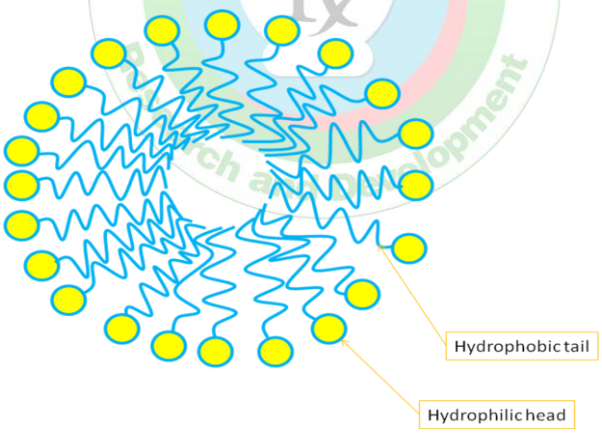

Figure 3: Structure of Polymeric micelles with labeling

Here are some of the recent pre-clinical studies or ongoing investigation on polymeric micelles that are used for the treatment of the cancer given the table (5):

Table 5: Some clinical studies on Polymeric micelles for the treatment of cancer

Names	Drugs	Diseases	References
Enzyme-responsive polymeric micelles	Cabazitaxel	Prostate cancer	103
Resveratrol loaded polymeric micelles	Resveratrol	Breast cancer	104
Targeted delivery nano polymeric micelles	Capecitabine, cyclodextrin	Colon cancer	105
Encapsulated polymeric micelles	Gambogic acid	Pancreatic cancer	106
Eradication of cancer stem cells	Doxorubicin, pluronic	Triple negative breast cancer	107

HYDROGEL SYSTEM:

Hydrogels, which have been known for some years, are insoluble crosslinked hydrophilic polymers that swell in aqueous media. Hydrogels are three-dimensional cross-linked polymeric networks having the potential to store a large quantity of water inside their porous structure. [72] According to the most popular definition, a hydrogel is a water-swollen, cross-linked polymeric network formed by a simple reaction of one or more monomers. Hydrogels are adsorptive materials made up of hydrophilic polymers joined together by chemical or physical cross-linking to absorb and hold enormous amounts of water inside their three-dimensional network without dissolving. [73] Hydrogels are a type of polymeric substance having physical and chemical characteristics that promote cell development. Tissue growth in artificial regenerative settings is widely recognized to need scaffolding platforms that give an overall microstructure that resembles the extracellular matrix. [74] The three-dimensional networks of hydrogels may absorb and hold considerable quantities of water in the cross-linked structures due to the hydrophilic functional groups connected to the polymer backbone. The resistance to breakdown of hydrogels is caused by cross-links between network chains. [75] Cross-linkage with low-molecular-weight hydrophilic polymers or oligomers has resulted in the formation of hydrogels. [76] Because the hydrogel system is constructed of polymer components that can be in a solution, suspension, or semi-solid state, it can undergo phase change at the site of administration immediately after administration, transforming the solution or suspension into a semi-solid or solid state.[77] The formation of hydrogels is typically governed by non-covalent intermolecular forces such as hydrogen bonding, π-π stacking, hydrophobic, dipole-dipole, and van der Waals interactions, the rational design and precise preparation of stimuli-responsive hydrogels produced by self-assembly processes remains a challenging research topic. [78]Hydrogels are network polymeric materials having highly hydrophilic polymer chains that may connect with enormous amounts of water without dissolving. The water might be strongly connected to the polymer network or free to flow within it. Hydrogels are biocompatible due to their high water content and may be manufactured with water contents comparable to biological tissues (70%) or considerably higher (up to and exceeding 99% water). [79] Small molecules in hydrogels have a high water content, flexibility, and diffusivity, making them ideal choices for simulating soft tissue microenvironments and acting as reservoirs for water-soluble cytokine and growth factor administration.[80]Recently, hydrogels with additional exceptional features, such as injectability, have been developed, allowing them to be conveniently supplied at the target region using minimally invasive methods. [81] Hydrogels are widely utilized in cancer radiation, chemotherapy, immunotherapy, hyperthermia, photodynamic treatment, and photothermal therapy because they have great biocompatibility, biodegradability, drug loading, and controlled drug release. In conclusion, hydrogel systems that have few side effects, are easy to administer, have a high local drug concentration, have sustained release qualities, and have minimally invasive provide tremendous promise for an all-encompassing therapy for cancer. [82] However, significant issues remain, such as ineffective encapsulation, simple leakage of loaded payloads, and a lack of controllability. [83] Cellular activities including adhesion, proliferation, spreading, migration, and differentiation may be regulated inside degradable, cell-compatible hydrogels by temporal adjustment of biochemical or biophysical signals like growth factor presentation or hydrogel stiffness. However, careful consideration of hydrogel base materials, formation chemistries, and degradable moieties is required to obtain the optimum level of property control and cellular response.[80]The structure of hydrogel system is shown in the figure (4) that is use for the treatment of cancer.

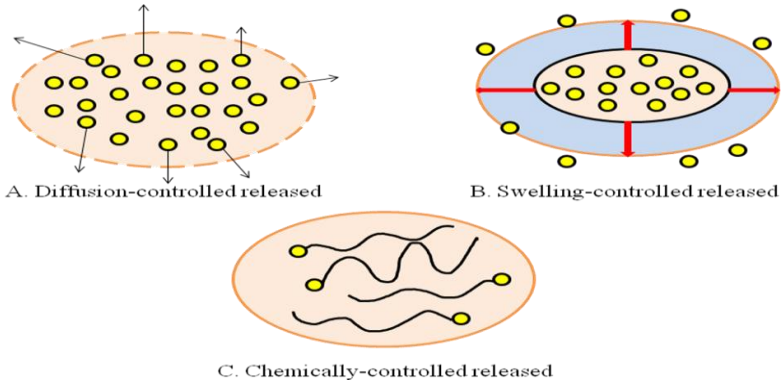

Figure 4: Structure of Hydrogel system with labeling

Here are some of the recent pre-clinical studies or ongoing investigation on hydrogel system that are used for the treatment of the cancer given the table (6):

Table 6: Some clinical studies on hydrogel system for the treatment of cancer

Names	Drugs	Diseases	References
RNA-triple helix hydrogel drug	RNA-triple-helix and siRNA duplexes of CXCR4	Triple negative breast cancer	108

Dual-drug delivery system	Methotrexate-loaded CaCO3 (CaCO3/MTX) and aspirin, alginate and sodium carboxymethyl cellulose	colorectal cancer	109
thermo-sensitive hydrogel system	Gemcitabine	bladder cancer	110
biodegradable thermo-sensitive hydrogel	Gemcitabine, cis-platinum	pancreatic cancer	111
injectable temperature-sensitive chitosan-based hydrogel	doxorubicin	colon cancer	112

With advancements focused on personalized medicine, combination therapies, targeted drug delivery, theranostics, immuno-oncology, overcoming biological barriers, biological sensing and imaging, reducing side effects, nanoparticle vaccines, and clinical translation, nanoparticles offer promising future perspectives in cancer nanomedicine. By customizing nanoparticle-based therapies to target certain tumor types, personalized medicine enables the development of therapeutic approaches that are based on the unique characteristics of each patient. Combination treatments improve treatment efficacy and eliminate drug resistance by combining many therapeutic ingredients into a single nanoparticle formulation. Using nanoparticles for targeted medication delivery makes it possible to precisely target cancer cells while protecting healthy tissues, reducing side effects, and enhancing results.

Novel nanoparticle compositions get beyond biological barriers like the blood-brain barrier to deliver treatments to previously unreachable tumor locations in a targeted manner. Nanoparticles are used as sensors to find biomarkers linked to cancer progression and therapy response, as well as contrast agents for sophisticated imaging modalities. Therapeutic compounds that are encapsulated in nanoparticles have less systemic toxicity, which reduces side effects and increases patient tolerance to therapy. Immunotherapy and cancer prevention might benefit from vaccinations based on nanoparticles. Preclinical and clinical research should continue because it will make it easier for nanoparticle-based treatments to go from the lab to the clinic, which will eventually help cancer patients all around the world.

CONCLUSION:

The use of nanotechnology to cancer therapy has ushered in a new age of cancer treatment. Several forms of NPs, including organic and inorganic NPs, are already widely employed in the therapeutic treatment of various cancer types. When compared to standard pharmaceuticals, NP-based drug delivery systems have better pharmacokinetics, biocompatibility, tumor targeting, and stability, while also helping to reduce systemic toxicity and overcome drug resistance.The selection of an optimal nanocarrier is not clear, and the few current comparison studies are difficult to interpret since numerous parameters may impact biodistribution and targeting at the same time. Furthermore, creating appropriate screening procedures for evaluating ideal nanocarrier properties remains hard.Research is still being conducted to reduce the toxicity of current nanocarriers and to investigate improved nanocarriers with a reduced toxicity profile.Nanoparticle's technologies offer enormous potential for converting poorly soluble, poorly absorbed, and labile physiologically active compounds into viable deliverable chemicals.As a result, over the last several years, many hybrid polymer nanoparticles have been developed to treat cancer. Nanoparticles have been developed in recent years for *in-vivo* cancer diagnostics, molecular biology screening of biological markers for malignancies, and targeted medicine administration. Such nanotechnology-based solutions might largely be utilized to treat different cancers.

CONFLICT OF INTEREST:

The author declares that there is no conflict of interest.

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