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"Development of a Novel Drug Delivery System for the Treatment of Cancer"

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ABSTRACT:
In recent times, the emergence of nanomaterials has led to the exploration of drug delivery systems as a novel approach to cancer treatment. Drug nanoparticles (NPs), a type of drug delivery system, offer numerous advantages over traditional antitumor drugs, including ease of preparation, high efficacy, low toxicity, and notably, the ability to actively target tumors. These drug delivery systems typically consist of delivery carriers, antitumor drugs, and sometimes target molecules. However, there is currently a lack of comprehensive research summarizing the application of drug delivery systems in tumor therapy. This review aims to provide an overview of the preparation, characteristics, and applications of various common delivery carriers, while also delving into the antitumor mechanisms of different antitumor drugs within these carriers. Ultimately, this review will contribute to a more solid theoretical foundation for the future clinical application of personalized cancer nanomedicine.

Keywords - Cancer Therapy, drug delivery system, anticancer drug, delivery carrier's, diagnosis, Nanoparticles.

I. INTRODUCTION

Novel drug delivery systems (NDDS) offer numerous advantages, such as enhancing therapy by boosting the effectiveness and duration of drug activity, promoting patient adherence by reducing the frequency of dosing, providing convenient routes of administration, and enhancing targeted delivery to minimize undesired side effects.

Significant progress has been achieved in recent years in the research and development of innovative drug delivery systems for anticancer medications (NDDS). Various new formulations such as polymeric nanoparticles, Nano capsules, liposomes, phytosomes, Nano emulsions, microspheres, and hydrogels have been documented utilizing bioactive compounds and plant extracts. [1]

Breast cancer (BC) remains the most common cancer with high mortality rates in women globally, as reported by the International Agency for Research on Cancer (IARC) with over two million new cases and around five million deaths in 2014. Despite significant progress in diagnosis and treatment, it continues to be one of the deadliest forms of cancer. The primary source of breast cancer (BC) is the epithelial cells lining the terminal duct of the lobule unit within the breast. BC can be categorized as non-invasive or in situ, where the cancer cells remain within the basement membrane of the draining duct and terminal duct of the lobular unit. Invasive BC, on the other hand, refers to the spread of cancer cells beyond the basement membrane into the surrounding normal tissues. [2]

Cancer continues to be a significant health issue in countries worldwide, including both developed and developing nations. The term "cancer" was initially coined by Hippocrates in 370 BC, referring to the abnormal growth of cells caused by chromosomal changes.Approximately 1.6 million cancer cases are reported annually in the United States alone. [3]

Ovarian cancer ranks as the fifth highest cause of cancer-related fatalities in women. It stands out as one of the most prevalent and lethal forms of gynecologic cancer, with 14,436 reported deaths in 2009. Projections estimate an incidence of approximately 21,980 cases and 14,270 deaths in 2014. [4]

Several types of nanoparticles with various structural and chemical compositions have undergone testing to assess their ability to target specific areas and serve as drug carriers. Numerous scientific studies have been conducted to evaluate the effectiveness of magnetic nanoparticles in treating brain tumor cells and breast cancer cells.

Additionally, colloid gold nanoparticles, liposomes, and polymeric micelles have been

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investigated as drug delivery systems to specifically target tumor cells and deliver anticancer drugs in a controlled manner. [5]

Numerous treatments have been created over the past fifty years to address challenging medical conditions. The increase in breast cancer cases may be attributed to changes in socioeconomic factors, including shifts in diet, occupational hazards, rising pollution levels, and environmental toxins. Furthermore, alterations in physiological aspects such as early menstruation, delayed menopause, shorter breastfeeding periods, and later first pregnancies have contributed to the higher prevalence of breast cancer. By managing modifiable risk factors, it is possible to prevent half of all breast cancer cases.[6]

The World Health Organization reports that cancer is the second most common cause of death worldwide, resulting in an estimated 9.6 million deaths in 2016. In Europe alone, there were 4.2 million newly diagnosed cases and nearly 2 million deaths attributed to cancer in 2018. Among the various types of cancer, breast, lung, colon, and prostate cancer were responsible for the highest number of fatalities in 2018. Overall, cancer-related deaths make up 20% of all deaths in Europe. [7]

Cancer poses a significant threat to human health and life, as highlighted in the 2020 WHO report on cancer. In 2018 alone, there were 18.1 million cases and 9.6 million deaths worldwide, making cancer the second leading cause of death globally. The incidence and mortality rates of cancer are on the rise, with projections indicating a potential doubling by 2040. Despite advancements in treatments such as surgery, chemotherapy, and radiation therapy, many patients, especially those in advanced stages, still face challenges in finding effective solutions. This has led to issues like tumor recurrence and metastasis. Exploring the cancer stem cells (CSCs) theory through research could offer promising new avenues for cancer therapy. [8]

Nanotechnology, a rapidly developing discipline, fulfills the requirements for groundbreaking methods in cancer diagnosis and treatment. These nanoparticles possess biocompatibility and biodegradability, comprising a core that serves as a carrier, along with functional groups on the core that specifically target designated areas. Drug delivery through nanotechnology encompasses various forms such as nanodisks, High Density Lipoprotein nanostructures, liposomes, and gold nanoparticles. [9]

Cancer remains a significant contributor to global mortality rates. The covert initiation of cellular elements that disrupt normal regulatory processes is what ultimately results in cancer formation. Nano-biotechnology emerges as an innovative method for delivering drugs, showing great promise in effectively and precisely targeting deadly cancers. A variety of biocompatible nanoparticle (NP)-based drug delivery systems, including liposomes, dendrimers, micelles, silica, quantum dots, and magnetic, gold, and carbon nanotubes, have already demonstrated success in targeted cancer therapy.[10]

Nano carrier's in Therapeutic Drug Delivery of Liver cancer

Recently, numerous studies have introduced different types of NCs for targeted drug delivery and imaging in liver tumors. Various nanocarriers utilized in drug delivery systems for liver cancer are illustrated in Figure 1. For instance, research has demonstrated the efficacy of polymeric micelles-doxorubicin NC in inhibiting the growth of HepG2 cell lines and improving survival rates in a HepG2 xenograft model.

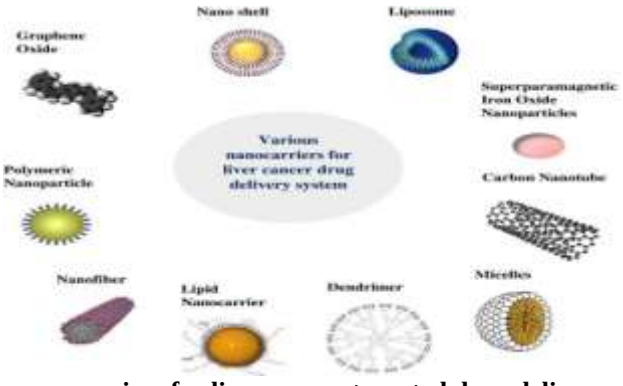

Fig-1 Various nanocarriers for liver cancer targeted drug delivery application's.

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Furthermore, the theranostic approach for liver cancer treatment is gaining increased attention and popularity. The list of nanocarriers utilized for liver cancer therapeutics and diagnostic purposes is presented in Table 1. Additionally, a variety of nanocarriers such as liposomes, micelles, dendrimers, metal oxide nanoparticles, nanocrystals, carbon nanotubes, magnetic nanoparticles, and nanogels have been employed in the treatment of liver cancer tumors, as outlined in Fig .1 [11]

DDS plays a crucial role in enhancing the effectiveness and safety of medications. Regardless of whether a drug is administered nasally, orally, systemically, or through other routes, it must traverse the surrounding tissue of the cancerous site once it enters the bloodstream. The tumor microenvironment, typically characterized by hypoxia and high interstitial fluid pressure, poses a physical obstacle that hampers the absorption rate of drugs in targeted tumor cells. This challenge is particularly significant in solid tumors due to the absence of functional lymphatic vessels and increased vascular permeability.

Terminology and biogenesis of EVs

EVs are produced and secreted by cells into the extracellular space as a result of various factors, including stimulation from growth factors and hormones, exposure to drugs or toxins, and stress.

EV- based drug delivery system

Just like the structure of lipid-based drug nanocarriers, the advancement of EV-based DDS is presently concentrated on enhancing effectiveness through modifications in their physical and biological characteristics to effectively target recipient cells and release their payload.

Targeting EVs to recipient cancer cell's

Enhancing the strategic delivery of chemotherapeutic drugs involves the precise targeting of drug accumulation solely at the tumor site, thereby enhancing the treatment's potency and effectiveness. [12]

Cancer treatment advancements continue to be a key area of interest for researchers globally. The advancements in this field present both a challenge and an opportunity for interdisciplinary collaboration to alleviate the pain of millions in the years to come. Despite the current effective treatment options, the mortality rate from cancer has been on the rise, partly due to the lack of vaccines and the recurrence of cancer in patients who have shown significant recovery. [13]

Doxorubicin

Doxorubicin, in its original state, has demonstrated significant therapeutic promise, being recognized as one of the most powerful chemotherapeutic drugs approved by the Food and Drug Administration.

Doxorubicin metabolism

Numerous investigations have been carried out to examine the pharmacokinetics of doxorubicin, focusing on its effectiveness in treating various types of tumors through single or multiagent therapy. The majority of these studies have demonstrated that after intravenous injection, the disposition of doxorubicin follows a multiphasic pattern. When administered intravenously, it is commonly accompanied by a triphasic plasma clearance. This indicates that doxorubicin is rapidly absorbed by cells, as evidenced by its distribution half-life of 3-5 minutes. On the other hand, the terminal half-life of doxorubicin, which ranges from 24 to 36 hours, suggests that the drug takes significantly longer to be eliminated from the tissue compared to its uptake.

Examples of molecular signals activated by and involved in doxorubicin action in normal and cancer cell's

Ongoing research is being conducted on the cellular mechanisms of chemotherapeutic agents to enhance cancer treatment. Studies have revealed that doxorubicin triggers AMP-activated protein kinase (AMPK) activation in embryonic ventricular myocardial H9c2 rat cells, leading to myocardial toxicity. The activation of liver kinase B1 (LKB1) by reactive oxygen species (ROS) serves as the upstream signal required for AMPK activation. Subsequently, doxorubicin-induced H9c2 apoptosis takes place. AMPK, a recently discovered protein kinase, functions as an intracellular energy status sensor, activated to conserve cellular energy and plays a crucial regulatory role in both cell survival and death during pathological stress conditions (such as osmotic, hypoxia, or oxidative stress). To exert its apoptotic effects, various downstream targets need to be modulated, including c-Jun N-terminal kinase (JNK), p53, and mTORC1 regulation. An illustration of this process can be observed in the apoptosis of insulin-producing MIN6 cells and 6

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cells, where AMPK activation leads to JNK activation, ultimately resulting in cell death in cultured cell. [14]Cancer is considered the most lethal disease affecting human beings worldwide. According to GLOBOCAN 2012, there were an estimated 14.1 million new cases of cancer each year globally, a number that is projected to increase to 19.3 million by the year 2025. The primary methods used for cancer treatment on a global scale include surgery, radiation, chemotherapy, and immunotherapy. However, these conventional therapies are associated with various drawbacks such as high toxicity, poor oral bioavailability, low water solubility, narrow therapeutic indices, inconsistent circulation, non-specific bio-distribution, and delivery of anticancer drugs to both healthy and cancerous cells. As a result, there is an urgent need for innovative, safe, and effective treatments to address the alarming rates of mortality and morbidity associated with cancer. [15]

Cancer is a result of abnormal and uncontrolled cell growth due to a lack of replication control. The delay in diagnosis and ineffective treatments are the primary causes of high mortality rates among cancer patients. Understanding the fundamental principles of tumor biology has led to significant progress in cancer management, diagnosis, and treatment in recent years. Traditional methods of cancer treatment include surgery, immunotherapy, radiation therapy, chemotherapy, and targeted hormone medications. However, these approaches are often limited in their effectiveness due to their lack of specificity, which can lead to adverse effects on healthy cells and the immune system. Additionally, drug resistance can develop in tumor cells with the use of all medications except surgery. Therefore, ongoing research is focused on developing new and improved ways to combat cancer. Drug tolerance remains a significant challenge in cancer treatment. Resistance to anticancer drugs can be either innate or inherited, leading to multidrug resistance where a patient becomes tolerant to multiple unrelated drugs. Tumors consist of replicating neoplastic cells and supporting stroma made of connective tissues and blood vessels. Different types of cancer include mixed tumors, tumors of parenchyma cells, mesenchymal tumors, and tumors originating from more than one germ cell layer. Carcinogens can be physical, chemical, or biological, with biological carcinogens including viruses, bacteria, and parasites. Carcinogenesis is influenced by endogenous chemicals from metabolic processes and cells carrying dormant viruses. Preventing the production, activation, and enhancing the elimination of carcinogens can help in cancer prevention. Common risk factors for cancer in humans include alcohol consumption, smoking, and dietary habits.

Chemotherapy is a medical treatment that involves the use of synthetic chemicals to combat cancer. Anticancer drugs can be administered alone or in combination to target and harm cancer cells, as well as inhibit tumor growth. However, one of the main challenges with chemotherapy is the occurrence of side effects caused by these anticancer drugs. These side effects arise due to the drugs' lack of specificity towards cancer-causing cells, affecting normal cells in the process.

In contrast, certain plant-based products have shown promise in cancer treatment with fewer side effects compared to conventional medications. Vinca alkaloids, taxanes, epipodophyllotoxins, camptothecins, genistein, and quercetin or rutin are examples of herbal medications associated with cancer treatment. Additionally, hormonal treatments, such as glucocorticoids, estrogen, progesterone, and gonadotropin-releasing hormone (GRH) analogs, have proven effective against certain types of cancer. Furthermore, radioactive isotopes, like radioactive iodine 131I, have a role in chemotherapy specifically for treating thyroid cancer.

Recent advancements in plant-based medicines and related research suggest that herbal medications for cancer treatment may potentially replace traditional chemotherapy and offer enhanced effectiveness against tumors.

The Role of Ayurveda in cancer Therapy

Ayurveda, an ancient medicinal plant system dating back 6000 years, is currently being used to treat and alleviate various types of cancer through the use of natural drugs and extract. The primary goal of Ayurvedic therapy in cancer treatment is to enhance the innate self-healing abilities of the mind. It not only aids in the identification of cancer but also provides valuable insights into herbal remedies and alternative treatments. Cancer-related illnesses not only impact physical health but also have a profound effect on mental well-being. Disharmony between the mind and body can manifest in symptoms such as fatigue, anxiety, restlessness, and depression. When cancer strikes, it disrupts the body and influences the Tamas (the energy that sustains all things over time) and the Kapha. Ayurveda offers a significant

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psychotherapeutic technique that has been utilized and is currently being implemented in various countries. Plants play a crucial role in medication, with vinca, shattering, guduchi, triphala, and tulsi being among the plants used as anticancer agents.

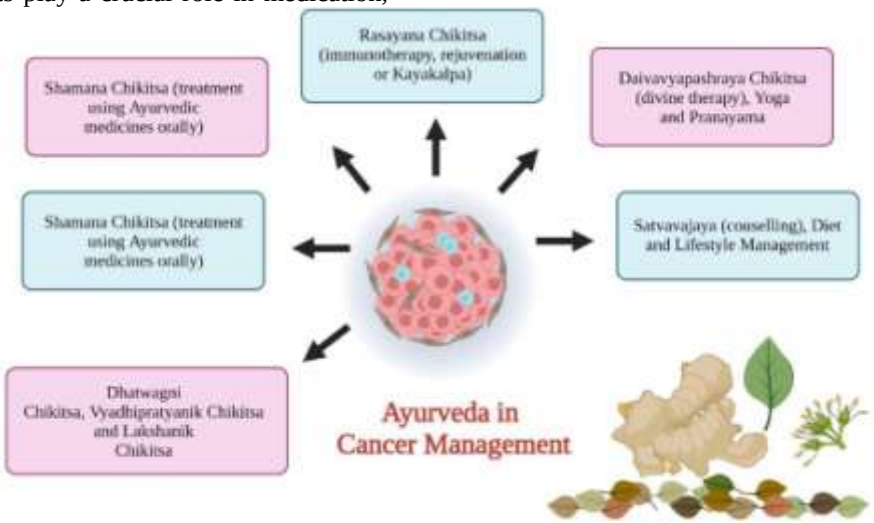

Fig-2 Different cancer management procedures in Ayurveda.

Herbal Plants Exhibiting Anticancer Activities

Human bodies consist of countless cells, with each cell functioning as an independent living organism. Regular body cells undergo a limited period of growth and replication before ceasing this process. Subsequently, they only replicate when there is a need to regenerate damaged or deceased cells. However, when the mechanism of cellular replication spirals out of control, it leads to the formation of a tumor. The abnormal growth and division of cancer cells are initiated by the destruction of DNA within these cells.

Drug Delivery Systems Entrapping Natural Bioactive Compounds For Cancer

Multiple novel drug delivery systems (NDDS) have been developed over the past two decades with the main objective of enhancing medication bioavailability, minimizing adverse effects, and preventing drug degradation. The concept behind a drug delivery system is to administer pharmaceuticals directly to the target area as per the body's requirement, while another delivery system is directed through drug delivery to the site of action. NDDS offer various advantages such as increased solubility, enhanced bioavailability, reduced unwanted side effects, improved therapeutic efficacy, enhanced stability, and optimized drug distribution. Furthermore, they play a crucial role in regulating pharmacokinetics, pharmacodynamics, and immunogenicity.

NDDS offer the advantage of increased patient convenience in drug administration. Drugs are released from these systems through passive and active targeting mechanisms.

We then filtered out components lacking strong literature support and focused on compounds with in vivo data evaluation, specifically targeting anticancer phytochemicals. Subsequently, we prioritized highly researched components with anticancer properties for further investigation. [16]

Intravesical administration is favored over systemic delivery for treating bladder cancer due to its effectiveness. Nevertheless, the frequent urination process can remove the drugs, leading to decreased drug levels. Additionally, the bladder's barrier hinders drug penetration into tumor cells. [17]

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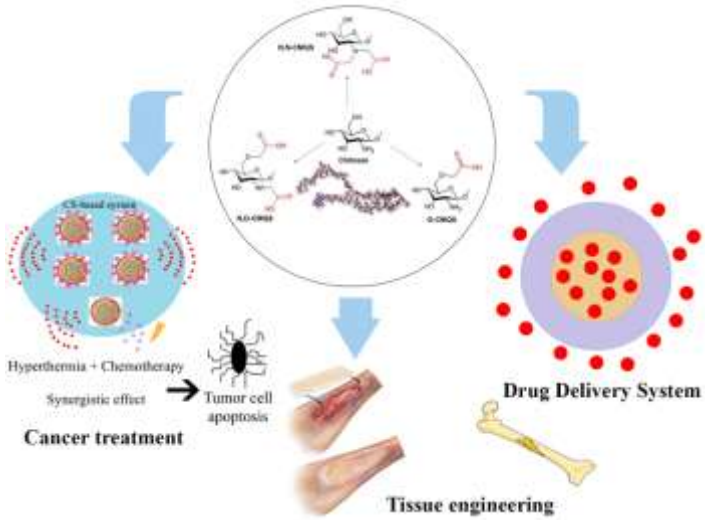

Fig-3 Tissue engineering drug delivery system and cancer Treatment

The recent focus on green technology has sparked research on biopolymers and bio-based polymers, which boast impressive physical and biological characteristics and are capable of biodegradation, unlike their synthetic counterparts. Chitosan serves as a prime illustration, being obtainable through the partial deacetylation of chitin, a natural polymer present in diverse organisms.

Chitosan, either on its own or when combined with other polymers or bioceramics, has been utilized recently in tissue engineering, drug delivery systems, and cancer treatment. When used as a scaffold, chitosan provides a physical framework for cells and tissues, aiding in tissue structuring and enabling numerous cells to be seeded, migrate, and proliferate. Additionally, it enhances osteoblast activity, mineralization, collagen production, tissue regeneration, and hemostatic properties, establishing chitosan as a key material in tissue engineering applications.

Chitosan exhibits inhibitory properties against the growth of tumor cells, tumor-induced angiogenesis, and tumor metastasis, thus demonstrating significant anticancer activity. The combination of chitosan-based systems with therapeutic metal ions (TMIs) and chemotherapy drugs can lead to a synergistic cytotoxic effect in cancer cells, enhancing the therapeutic potential and effectively reducing tumor cell proliferation. This approach also contributes to the acceleration of tumor shrinkage and disappearance. Moreover, chitosan has the ability to activate dendritic cells (DCs), which in turn initiate innate immune responses. It facilitates communication between DCs and natural killer (NK) cells, promoting the survival and enhancing the effector functions of human NK cells. Consequently, chitosan exhibits in vivo antitumor activity.

Chitosan and its derivatives have demonstrated remarkable efficacy in tissue engineering, drug delivery systems, and cancer treatment. Over the past decade, there has been a notable surge in research focusing on these applications. Nevertheless, a dearth of comprehensive reviews exists regarding the latest literature in these specific areas of chitosan application. This dearth has served as the impetus for the creation of the present review article.

Chitin and Chitosan

Chitin, the second most abundant organic compound found in nature, is a semi-crystalline polysaccharide composed of β-(1→4)-2-amino-2-deoxy-D-glucose and β-(1→4)-2-acetamide-2-deoxy-D-glucose monomeric units. It is a biological polymer made up of glucosamine and N-acetylglucosamine monomers connected by β-(1→4)-glycosidic bonds. The average molar weight of native chitin typically exceeds 106 Daltons, and this substance possesses intriguing characteristics such as biodegradability, antibacterial properties, non-toxicity, and the ability to form gels. Chitin is sourced from a wide range of organisms, with shrimps, crabs, and crawfish being the primary sources, although it also naturally occurs in certain species of insects, fungi, and yeast.

Chitosan possesses a range of noteworthy biological properties, including antimicrobial, antibacterial, antifungal, antitumor, and hemostatic

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activities, as well as clotting time reduction, mucoadhesion, analgesic effects, acceleration of healing, treatment of osteoarthritis, hypocholesterolemic and hypolipidemic effects. The antibacterial and antifungal activities of chitosan are attributed to two main mechanisms described in the literature. The first mechanism involves the interaction between negatively charged groups on the cell surface and positively charged chitosan, altering cell permeability to prevent the entry of essential materials or the leakage of important solutes. The second mechanism involves the binding of chitosan's protonated amino groups to cell DNA, inhibiting microbial RNA synthesis. These inherent antibacterial and antifungal properties of chitosan and its derivatives make it a suitable component in commercial disinfectants, effectively inhibiting the growth of a wide range of fungi and bacteria. Moreover, chitosan exhibits a broad spectrum of activity and is less toxic to mammalian cells compared to other disinfectants.

Chitosans Chemical Modification

The transformation of chitosan into its oligosaccharides has been thoroughly researched in the field of biology due to their specific biological properties, including antitumor effects, immunostimulatory effects, enhancement of protective mechanisms against certain pathogens in mice, antifungal and antimicrobial properties, radical scavenging capabilities, and the anticoagulant properties of chitosan polysulfate derivatives as documented by various scientists.

The chemical alteration involving the substitution of hydroxyl and amino groups in chitosan with sulfate can lead to structural diversity in the polymer chain (with structures being randomly dispersed), revealing suitable attributes for biological purposes. Sulfated chitosan and its derivatives containing N and/or O-sulfate groups, sometimes in combination with other components, have been extensively evaluated as potential heparin-like substances, demonstrating anticoagulant, antitumor, anti-sclerotic, and antiviral effects. Research has indicated a notably high anticoagulant efficacy in comparison to conventional therapeutic heparin. [18]

Cancer is a leading cause of death worldwide, and its development is often due to the activation of cellular factors that disrupt normal regulatory pathways. In the field of nano-biotechnology, there is great potential for using drug-delivery systems to effectively and accurately target lethal cancers. Various biocompatible nanoparticle (NP)-based drug-delivery systems, such as liposomes, dendrimers, micelles, silica, quantum dots, and magnetic, gold, and carbon nanotubes, have already shown success in targeted cancer treatment. These NPs are modified with biological molecules, peptides, antibodies, and protein ligands to enhance targeted drug delivery. These systems typically consist of a hydrophilic central core, a biocompatible outer layer that is designed to target specific sites, and a hydrophobic core where the drug is housed. The structural integrity of NPs allows them to adapt to the cancer microenvironment, making them ideal vehicles for targeted drug delivery. However, the tumor microenvironment (TME) can pose challenges to drug delivery due to its complex nature. Despite this, successful interaction between NPs and the TME can result in targeted drug release. Currently, there are several drugs and NP-based delivery systems for cancer undergoing clinical and preclinical trials, with some already approved by the Food and Drug Administration (FDA), such as taxol, doxil, cerubidine, and adrucil. This review provides an overview of the latest advancements in cancer treatment drugs, their NP-based delivery systems, and the role of the TME in this context. [19]

An Overview of gold Nanoparticles

Gold has been utilized for its medicinal properties since ancient times, particularly in India and China, where it was associated with longevity and fertility. Even today, gold is still used in certain ayurvedic preparations in India. Throughout the middle ages and into modern times, gold has been employed in the treatment of neurological disorders and syphilis. In the 20th century, gold was utilized in the treatment of tuberculosis and rheumatic diseases. The healing attributes of gold nanoparticles were first documented in the 17th century by the philosopher and physician Francisci Antonii in his book, where he detailed the creation of colloidal gold and provided information on its medical applications.

Gold nanoparticles consist of a core made of gold surrounded by a protective outer layer of organic ligands. Among metallic nanoparticles, they have been proven to be the safest and least toxic agents, possessing exceptional optical, plasmonic, and magnetic properties, as well as a large surface area. Their ease of modification and the ability to load them with drug therapies make them an ideal vehicle for drug delivery. Over the

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years, advancements have been made in synthesizing particles of controlled sizes and incorporating multifunctional monolayers. Additionally, ligand place-exchange reactions enable these monolayers to contain multiple targeting agents and/or drugs, such as small molecules, peptides, proteins, antibodies, or oligonucleotides.

The evolution of cancer pharmacological treatment and the rise of targeted therapies.

Cancer chemotherapy originated in the 1940s with the discovery of the alkylating activity towards DNA of nitrogen mustard. Currently, cyclophosphamide is the primary nitrogen mustard utilized in cancer therapy. Additionally, various other alkylating agents like carmustine, busulfan, thiotepa, dacarbazine, cisplatin, carboplatin, and oxaliplatin are employed in cancer chemotherapy. In 1947, the impact of the folic acid analog "aminopterin" on acute lymphoblastic leukemia was noted. Subsequently, other antimetabolites such as methotrexate, mercaptopurine, fluorouracil, gemcitabine, and capecitabine have become essential components of cancer chemotherapy. In the late 1950s, natural antimitotic agents derived from Catharanthus roseus were identified. Notably, vinblastine, vincristine, and vinorelbine are still widely used in chemotherapy. Furthermore, antimitotics like Teniposide and Etoposide from Podophyllum peltatum, topotecan and irinotecan from Camptotheca acuminate, and paclitaxel from Taxus brevifolia, discovered in the 60s and 70s, continue to be integral in cancer treatment. Actinomycin D, the first antibiotic with cytotoxic properties, was found in 1940, followed by daunorubicin in 1963, bleomycin in 1966, and doxorubicin in 1968. These highly effective products, derived from fungi and bacteria, remain crucial in current cancer treatment. [20]

The Peritoneal cavity has long been recognized as a common site for the spread of various intra-abdominal malignancies, including stomach, colon, pancreas, and rectal cancer. Initially, it was believed that achieving a curative treatment was impossible. However, this notion was challenged with the introduction of cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC). While the effectiveness of these treatments has been demonstrated both in experimental and clinical settings, there is still room for improvement. Firstly, a significant number of patients experience recurrent disease. Secondly, the use of HIPEC requires specialized perfusion devices that are not readily available in most hospitals. As intraperitoneal administration of chemotherapy is believed to be crucial, new methods for delivering effective chemotherapeutic agents to the peritoneum are being developed. This review aims to provide an overview of the experimental data on novel drug delivery systems (DDS) for peritoneal cancer. [21]

Liposomes represent biodegradable and biocompatible lipid bilayer vesicles that serve as highly effective carriers for delivering both hydrophobic and hydrophilic bioactives. The structural design of liposomes, including ligand anchoring, prolonged circulation, and responsiveness to stimuli, continues to evolve to address the growing demands of clinical and industrial applications. Recent research highlights the emergence of multifunctional liposomes for integrated theranostic approaches in cancer therapy. This overview provides valuable insights into the progress made in ligand-targeted liposomes (such as folate, mannose, transferrin, hyaluronic acid, antibodies, aptamers, peptides, etc.), stimuli-responsive liposomes (in response to pH, temperature, hypoxia, etc.), liposome-mediated autophagy modulation, and theranostic liposomes for cancer diagnosis and treatment. Additionally, it covers patents, clinical trials, and commercially available liposomal products. This compilation of advancements will undoubtedly be of interest to aspiring scientists and pharmaceutical companies involved in liposome development.

Long Circulatory Liposomes

The primary challenge in utilizing liposomes as a potential drug delivery system lies in their uptake by the ABC and RES. The presence of opsonins in the blood leads to the rapid opsonization of liposomes. Numerous efforts have been made to evade the RES uptake of liposomes and prolong their circulation time by altering their size or modifying their surface. The second generation liposomes, on the other hand, are a variant of modified liposomes in which their surface is altered through the use of glycoprotein and oligosaccharides.

Targeted Liposome

The third generation liposomes, known as targeted liposomes, are created by modifying their surface with appropriate ligands. These liposomal systems offer the potential for both active and passive targeting. In the case of passive targeting, liposomal formulations exhibit a greater

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concentration of the drug within tumor cells due to the enhanced permeability and retention (EPR) effect. Additionally, the third generation liposomes possess active and physicochemical targeting capabilities. Functionalized liposomes have the ability to achieve targeted drug delivery. [22]

Cancer remains a significant contributor to morbidity and mortality on a global scale, regardless of the level of human development. In 2020, there were an estimated 19.3 million new cases of cancer and nearly 10 million cancer-related deaths worldwide. The critical role of prevention, early detection, and effective cancer treatments cannot be overstated. Targeted drug delivery to specific tumor sites is a key strategy in cancer therapy, with nanogels emerging as a promising drug delivery system. Nanogels, characterized by their dual hydrogel and nanoparticle properties, offer great potential as targeted drug delivery systems in cancer therapy. With a tunable porous structure and nanoscale particle size ranging from 20 to 200 nm, nanogels are envisioned as ideal drug delivery systems due to their high drug loading capacity and stability. By incorporating active targeting mechanisms and responsiveness to internal or external stimuli like pH, temperature, or light, nanogels enable controlled drug release, minimizing side effects and preventing accumulation in non-target tissues. Chemically cross-linked or physically assembled nanogel systems are particularly suitable for delivering drugs with severe adverse effects, short half-lives, and susceptibility to enzymatic degradation, such as anti-cancer drugs and proteins. This review provides an overview of the evolution of nanogels in targeted drug delivery for cancer therapy over the past decade, including current clinical trials and recent applications in this field.

Cancer epidemiology

Cancer poses a significant threat to humanity, encompassing a wide range of diseases that can impact any area of the body. One of the key characteristics of cancer is the rapid growth of abnormal cells that exceed their normal boundaries, leading to the destruction of surrounding tissues and potential spread to other organs. Metastasis, the process by which cancer spreads, is a primary cause of death related to the disease. Terms such as neoplasm, malignant, and tumor are often used to describe this condition. In 2020, cancer was responsible for nearly 10 million deaths globally, playing a crucial role in shaping life expectancy across all countries. According to the World Health Organization (WHO), cancer ranks as the leading or second leading cause of death before the age of 70 in 112 out of 183 member countries. The increasing incidence and mortality rates associated with cancer worldwide can be attributed to factors such as population growth, aging demographics, and changes in the prevalence of key risk factors linked to socioeconomic development. Recent estimates from GLOBOCAN in 2020 indicate a temporary decrease in cancer cases and deaths, influenced by various factors including delays in diagnosis and treatment due to the COVID-19 pandemic, which resulted in disruptions to healthcare services and screening programs.

Available Cancer Therapies

The primary goal of exceptional research following the discovery of malignancy is to identify effective treatment methods for cancer using innovative approaches. Currently, more than 60% of treatment trials worldwide are focused on cancer. The selection of treatment method and its efficacy are influenced by the type of cancer, its location, and the stage of progression. Traditional cancer treatment involves various procedures, including diagnosis and therapy, which are time-consuming and consequently expensive. Common methods of traditional cancer treatment include radiation-based surgical tools, surgery, chemotherapy, and radiotherapy. Modern modalities in cancer treatment encompass stem cell therapies, immunotherapy, anti-angiogenic therapy, hormonal-based therapy, targeted therapy, dendritic cell-based immunotherapy, and combination regimens. The integration of diagnosis and therapy into a single system, known as cancer theranostics, has demonstrated significant potential in the realm of cancer treatment.

Chemotherapy

Chemotherapy plays a crucial role in cancer treatment, serving as a key tool in fighting against the disease. By inducing apoptosis and inhibiting the division of cancer cells, chemotherapeutic agents effectively halt tumor progression. However, the toxic nature of chemotherapy can lead to increased vulnerability to other illnesses and negatively impact the bone marrow, ultimately weakening the immune system. While healthy cells normally undergo a process of renewal and regulation, chemotherapeutic agents disrupt this balance by either causing cell death or halting cell growth, categorized as cytotoxic and cytostatic effects. Unfortunately, the targeting of

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normal cells by chemotherapy can result in severe side effects including compromised immunity, hair loss, vomiting, nausea, weakness, susceptibility to infections, and in some cases, even death.

Cancer Immunotherapy

Cancer immunotherapy is comprised of several essential processes and has rapidly evolved into a promising strategy for cancer treatment. The cancer-immunity cycle encompasses the release of cancer antigens, the presentation of these antigens by antigen-presenting cells (APCs), the priming and activation of T cells, the infiltration and migration of T cells to tumors, and ultimately the recognition and elimination of tumor cells by cytotoxic T cells. Current approaches to cancer immunotherapy mainly involve therapeutic antibodies, adoptive cell therapy, and cancer vaccines, which may represent potential therapeutic targets utilizing diverse methods.

Nanogels For Cancer Therapy

In the past few years, nanogels have emerged as promising drug delivery systems to address the limitations of existing conventional cancer treatments. Section will delve into the characteristics of nanogels and explore their role as targeted drug delivery systems in cancer therapy.

Application's of nanogels as improved drug delivery systems for cancer Therapy

Nanogels have been demonstrated to be an outstanding drug delivery system that can address the limitations of traditional anti-cancer treatments and enhance the outcomes of cancer therapy. For example, the lack of selectivity in conventional chemotherapy, which affects both cancerous and healthy cells, results in heightened adverse effects and toxicity. Stimuli-sensitive nanogels have been developed and tested successfully for the targeted delivery of chemotherapeutic agents to cancer cells, minimizing adverse effects and toxicity. While hormone therapies are effective for hormone-related cancers, some of these therapies have been linked to an increased risk of diabetes and blood clots. Nanogels designed for targeted drug delivery in such cancer types do not pose these risks. Chitin-polymerized doxorubicin-loaded nanogels have been effectively used in treating breast, liver, prostate, and lung cancer. Although cancer immunotherapy represents an advancement over traditional cancer treatments, there are various physical barriers and metabolic factors that hinder optimal cancer immunotherapy, which are not present in nanogel applications. Furthermore, cancer immunotherapy may lead to increased toxicity in healthy cells. In 2018, researchers succeeded in creating protein nanogels to deliver precise amounts of chimeric antigen receptor (CAR) T-cells for immunotherapy. These nanogels were engineered to release CAR T-cells into the tumor microenvironment in response to T-cell receptor (TCR) activation. The controlled release of proteins ensured the effective delivery of drug cargo, enhancing efficacy without increasing toxicity. [23]

Despite the progress in treatment methods, colon cancer (CC) remains the third most common cause of cancer-related deaths globally. The adverse effects resulting from the toxicity of traditional drugs pose a significant challenge in chemotherapy. Efforts are being made towards delivering chemotherapeutic drugs directly to the affected area of the colon in a reliable and predictable manner.

Recent Developments in nanodrug formulation for treatment and prevention of CC.

Lately, numerous drug-conjugated nanosystems targeting the colon have been created to address CC. Nutlin-3a, a hopeful antineoplastic medication, faces various challenges like poor solubility, non-targeted delivery, toxicity, short circulation time in tumor tissue, expulsion by transmembrane proteins, and degradation by cellular lysosomes, leading to a suboptimal drug reaction. Nutlin-3a works by inhibiting the inactivation of the p53 tumor-suppressing protein.

Liposomes

Recently, there have been many drug-conjugated nanosystems developed to target the colon in order to combat CC. Nutlin-3a, a promising antineoplastic drug, encounters several obstacles such as low solubility, lack of targeted delivery, toxicity, limited time in circulation within tumor tissue, elimination by transmembrane proteins, and breakdown by cellular lysosomes, resulting in an inadequate drug response. Nutlin-3a functions by preventing the deactivation of the p53 tumor-suppressing protein. [24]

Cancer is currently the primary cause of death in various populations worldwide. Treatment options are limited to chemotherapy, radiation, and surgery. Nanoparticles-based drug delivery systems allow for selective targeting of tumor cells, maximizing drug concentration at the desired site while protecting surrounding healthy tissues. To

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enhance the targeting potential of anticancer drugs, nanoparticles are optimized for size and surface characteristics to improve circulation time and targeting efficiency. Passive targeting involves surface modification with polyethylene glycol to evade elimination by the body's defense mechanisms. Active targeting, on the other hand, involves chemical interactions with specific antigens, receptors, and genes that are overexpressed during disease progression. Recent advancements in "smart" stimulus-responsive drug carriers aim to improve the localization and efficacy of therapeutic payloads compared to free drugs. Multi-functional nanocarriers offer enhanced targeting potential, imaging capabilities, and controlled release of drugs or therapeutic molecules, promising a significant increase in the effectiveness of diagnostic and therapeutic applications in pharmaceutical sciences. [25]

Contemporary healthcare is not solely a result of our enhanced comprehension of biological mechanisms but also heavily relies on technology to unveil and capitalize on this profound understanding. Nanotechnology elevates this endeavor to the submicroscopic realm, utilizing tools like nanoparticles engineered at the subcellular level. This article offers a summary of the latest nanovectors and drug delivery systems. It discusses the advantages and safety issues associated with nanoparticles and nanomaterials, as well as their current and future applications in clinical medicine. The integration of nanomedicine in treating CNS diseases will rely on continued progress in nanotechnology and image-guided therapy.

Cancer diagnosis and Treatment

The National Cancer Institute (NCI) acknowledges the significant promise of nanotechnology in the field of cancer diagnosis and treatment, as highlighted by Cuenca et al. (2006). The establishment of eight nanotechnology centers in prominent academic institutions across the United States was a result of NCI's Centers of Cancer Nanotechnology Excellence initiative in 2005. These centers have been dedicated to enhancing nanoscale drug delivery systems, including liposomes, gelatin nanoparticles, polymeric nanoconjugates, and micelles. [26]

According to the World Health Organization (WHO), cancer is a leading cause of death globally, resulting in an estimated 9.6 million deaths in 2018. In 2020, the most prevalent fatal cancers included lung (1.76 million deaths), colorectal (862,000 deaths), stomach (783,000 deaths), liver (782,000 deaths), and breast (627,000 deaths) (IARC, 2020). Regrettably, treatment options are restricted due to the diverse nature of the disease, dose-dependent toxicity, and side effects (Olov et al., 2018, Saklani and Kutty, 2008). An encouraging approach to mitigate the adverse effects of these treatments involves targeted therapy utilizing nanoparticles (NPs) and hydrogels, which can encapsulate, protect, transport, and deliver therapeutic agents (Pandey et al., 2014). Encapsulated drug delivery systems also enable the release of appropriate concentrations in specific areas, enhancing the efficacy against cancer cells while minimizing side effects and toxicity in healthy cells. Although only a limited number have been authorized, these systems are expected to play a growing role in cancer treatments in the future (Iturrioz-Rodríguez et al., 2019, Sunderam et al., 2019). Presently, there are 94 approved cancer treatment drug delivery systems available for purchase, comprising 81 nanoparticles and 13 hydrogels.

Polyvinyl alcohol properties

PVA is a man-made polymer with the chemical formula $(C_2H_4O)_n$. Depending on the length of the original vinyl acetate polymer and the extent of hydrolysis, PVA products can exhibit varying molecular weights ranging from 20,000 to 400,000 g/mol. These products are categorized into two groups: partially hydrolyzed and fully hydrolyzed.

PVA in Biomedical area

A polymeric drug delivery system must surpass the limitations and drawbacks associated with traditional therapeutic agents. It should possess the qualities of being biodegradable, biocompatible, and non-toxic. The prominent delivery systems include hydrogels, microparticles, and loaded polymeric nanoparticles. Extensive research has demonstrated that the distinct properties of polymers play a pivotal role in their suitability for specific targets.

PVA future trend forecast

Historically, PVA has been utilized in the synthesis and advancement of nanomaterials for drug delivery in the field of oncology. Nevertheless, the recent progress in biomedicine has unveiled novel therapeutic molecules, including growth factors, proteins, peptides, and nucleic acids, which necessitate a more

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sophisticated drug delivery system. Consequently, there is a need to develop new pharmaceutical excipients and their corresponding delivery systems that can enhance the efficacy of drug administration. [27]

The pursuit of an optimal cancer treatment has led to the investigation of various platforms to improve the efficiency of drug delivery. As a result, there has been a growing interest in exploring different natural particles and biomaterials for this purpose. It will also examine recent innovative examples, their benefits and limitations, and their potential for future clinical use. [28]

The treatment of malignancies has experienced significant transformations in recent decades. The advancements in drug delivery techniques and nanotechnology have paved the way for novel formulations of existing drugs. These advancements aim to enhance the pharmacokinetics, increase accumulation in solid tumors, and minimize the adverse effects of these crucial therapeutic agents. In this review, we examine the published clinical data on cancer therapy using various major drug delivery systems. Furthermore, we address the challenges associated with effective cancer therapy through drug delivery, such as physical barriers, tumor heterogeneity, drug resistance, and metastasis. [29]

Nanotechnology in medicine

Recent advancements in the field of medicine and healthcare have significantly enhanced the lifespan of individuals. However, this prolonged lifespan has also led to an increased susceptibility to various types of cancer, as cancer is predominantly associated with old age. Additionally, as individuals age, they often develop multiple health conditions alongside their cancer diagnosis. Consequently, there is a growing demand for the development of new therapeutic agents that effectively target cancer while addressing these associated risks. Currently, chemotherapy utilizing cytotoxic agents remains the primary approach for treating numerous malignancies.

Limitations of current cancer treatment modalities

At present, the chemotherapy drugs that are available have been proven effective over time and provide a satisfactory period of disease-free survival. However, their usefulness is limited due to the toxicity they pose to non-target tissues and the development of drug resistance.

Contributions from basic cancer Biology for drug delivery

Studies conducted in the realm of molecular oncology, which focuses on fundamental disease mechanisms, have revealed six significant attributes of tumor cells, commonly known as the "hallmarks of cancer". One of these characteristics is sustained angiogenesis, which signifies that tumors establish their own blood supply by utilizing the pre-existing vessels of the host organism for nourishment. [30]

Nano drug delivery system in Bladder cancer

Various types of nano drug delivery systems, including liposomes, polymeric nanoparticles, magnetic nanoparticles, silica nanoparticles, protein nanoparticles, metallic nanoparticles, cationic nanoparticles, and carbon nanoparticles, have shown promise in both diagnosing and treating cancer. [31]

The Cancer Burden in the world

The National Cancer Institute provides a definition of cancer as a collection of diseases characterized by uncontrolled division of abnormal cells that have the ability to spread to different tissues. This uncontrolled growth can occur in various parts of the body, resulting in a diverse array of cancer types. [32]

Nanomedicines in cancer Therapy

The development of nanomedicines for the treatment and diagnosis of cancer is still in its early stages. Within the field of medicine, nanotechnology involves the utilization of precisely designed materials to create new therapies and devices that minimize toxicity and enhance the effectiveness of drug targeting within tumor tissues, as opposed to traditional chemotherapy methods. [33]

Over the past few years, there has been increasing recognition of the significant potential of synthetic polymers in serving as carriers for drugs. By encapsulating cancer drugs within polymeric micelles that have been tailored for cancer targeting and triggered release, the efficiency of drug delivery is significantly enhanced. [34]

Challenges in cancer Treatment

Cancer is a significant contributor to mortality worldwide. While localized primary solid

tumors can be effectively eliminated through surgical procedures, the management of spreading tumors and tumor metastases necessitates extensive chemotherapy. The administration of anticancer medications is often accompanied by various side effects, notably nephrotoxicity, neurotoxicity, ototoxicity, and others. [35]

Nanorobotics, envisioned as a remarkable advancement in future medicine, are sophisticated submicron devices primarily composed of bio-nanocomponents. They hold great promise in the field of drug delivery, particularly in targeting cancer, which is the primary cause of death in individuals under 85 years of age. These nanorobots have the potential to transport and administer significant doses of anti-cancer medications directly to cancer cells, while minimizing damage to healthy cells, thereby decreasing the adverse effects associated with traditional chemotherapy. [36]

Chemotherapy stands as a crucial treatment option amidst the array of available approaches. However, the current state of chemotherapy falls short of satisfaction. Its effectiveness is constrained, and patients endure severe side effects, some of which pose life-threatening risks. The emerging methods of cancer treatment not only complement traditional chemotherapy but also strive to safeguard normal tissues and combat drug resistance. The advancement in cancer treatment necessitates fresh perspectives on drug delivery. [37]

II. CONCLUSION

Drug delivery system are regarded as highly promising tools in the field of cancer treatment, offering oppurtinities for intricate multifunctional and targeted approaches.Among the extensively researched drug delivery ssystems are CMC NPs, BSA NPs, HFt NPs, liposomes, exosomes,dendrimers, PSiNPs, GO, AgNPs, and AuNPs. The utilization and advancement of these system can enhance the solubility and permeability of antitumor drugs, augment the retension effect, prolong the circulation half-life, improve the biological distribution, and mitigate toxicity. Consequently, they hold significant research value in enhancing treatment strategies for cancer patients through personalized cancer nanomedicine.

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