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DEVELOPING A NOVEL DRUG DELIVERY SYSTEM FOR TARGETING CANCER CELLS

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Abstract
Nowadays, surgically excising the tumor bulk is the main goal of most cancer treatment regimens. Examples of physical and chemically based treatments that have considerably inhibited the proliferation of cancerous cells include radiation therapy and chemotherapy. Furthermore, quality of life is diminished by these medicinal techniques' significant side effects and increasing toxicity. In order to enhance prognosis, this review addresses new methods for more efficiently administering chemotherapy. Nowadays, there is a lot of activity in the field of cancer therapy, and significant advancements are being made in the creation of novel cancer medications. New techniques such as ligand or receptor-based targeting, triggered release, intracellular drug targeting, gene delivery, cancer stem cell therapy, magnetic drug targeting, and ultrasound-mediated drug delivery stand in contrast to conventional cancer treatments. These techniques have made it possible to identify and eradicate cancer cells precisely while causing negligible or no adverse effects. Using influx transportation to deliver medications to cancer cells at specific locations and minimizing or eradicating multi-drug resistance are essential elements of the cancer therapy approach.
Keywords: novel approaches, malignant cells, influx transportation

1. INTRODUCTION

A group of illnesses known as cancer are defined by the unchecked development and spread of cancerous cells [3]. These cells undergo a transformation that gives them the ability to replicate indefinitely, which allows them to spread to other organs and cause cancer. The patient usually dies as a result of uncontrolled or ineffective prevention of such cancer cell spread [1]. Nearly one out of every four deaths in the US are caused by cancer, making it the leading cause of mortality [2]. While inherited genetic changes, immunological problems, and hormones are internal causes, infectious agents, poor food, pesticides, environmental contaminants, and tobacco are external factors. In order to start treatment, diagnosis and staging are essential. Chemotherapy, radiation, and surgery are the conventional methods of treating cancer [11]. malignant therapy is a multidisciplinary undertaking due to several differences between normal and malignant biology. It has shown to be very difficult to optimize efficacy and minimize harm through targeted therapy depending on different tumor types. Targeted therapy hasn't worked successfully for some tumors. The Cancer Genome Atlas (TCGA) was developed to investigate possible approaches to offering a comprehensive classification system.
Remarkably, 12 cancer types were concordantly classified into 11 broad subgroups by TCGA's integrative analysis. Based on their mutational information from 3281 tumors, the following 11 cancer types were normalized: Analysis revealed that whereas some cancers are homogenous, others are molecularly heterogeneous. As was previously mentioned, there are 100 different varieties of cancer that fall under the broad categories of histological classification, which include carcinoma, sarcoma, myeloma, leukemia, lymphoma, and mixed types. To have an effective cancer therapy, it is desirable to enhance and create new methods for the effective delivery of chemotherapeutics to cancer cells. Conventional chemotherapy medicines aggregate in both malignant and normal cells due to their non-specificity. The ultimate goals of cancer treatment are to improve quality of life and reduce systemic toxicity. The landscape of cancer treatment has changed significantly over the last four decades[16]. Drug-induced toxicity, non-specificity, and embolism may all be

linked to direct drug administration [4]. Additionally, for an oral medication regimen to reach the therapeutic level in cancer cells, it must first pass metabolism, overcome biological barriers, and bind to proteins. When cancer is benign, medications can be delivered directly to the tumor microenvironment. However, as cancers spread and infiltrate neighbouring normal tissues, the picture completely changes. Under these conditions, tumor cells change their phenotype (metastasis) and spread to other organs. These cells also overexpress metabolizing enzymes and efflux pumps (P-glycoprotein, MRP, and BCRP) in comparison to normal cells [12].

2. REVIEW OF LITERATURE

One effective method of medication delivery is ligand/receptor targeting [9]. Chemotherapeutic medications must reach the tumor cells' cytoplasm or subcellular organelles like the mitochondria and nucleus for maximum efficacy. Proper ligand design, customization, and selection can accomplish this kind of targeting [10]. Antibodies must be specific in order to target an antigen that is overexpressed in cancer cells. However, the drug release mechanism at the cancer location is equally crucial. A drug's early release could be hazardous to the entire body. Aptamers, siRNA, peptides, and antibodies are examples of tumor homing ligands that target metastatic cells in an effort to stop invasion and migration. Targeted medication delivery comes in two flavors: active and passive [5]. Drug delivery using ligands is one facet of active targeting.Passive targeting takes advantage of the tumor architecture's systemic and lymphatic networks. A number of anticancer drug delivery targeting strategies have been devised, some of which are addressed in this review article [15].

Monoclonal antibodies against different antigens greatly expressed on cancer cells are a new strategy. ADC is a general category of potent biopharmaceutical drugs developed for targeted treatment like cancer. Antibodies can specifically target cancer cells that express a particular antigen. Some antibody drug conjugates, including brentuximab devotion and trastuzumab emtansine, have been marketed as cancer treatments. While most antibody drug conjugates are already in various phases of clinical trials, other biologics are still in the early stages of research. Robertson et al. investigated recombinant human interleukin 18 (rhIL-18), an anticancer cytokine coupled to Rituximab [6]. Non-Hodgkin lymphoma can be effectively treated with this B cell lymphoma CD20 monoclonal antibody. Phase I investigations showed a baseline lymphocyte count, a short lymphopenia, and increased plasma levels of pro-inflammatory cytokines in 19 patients receiving intravenous rituximab (375 mg/m2/wk) and rhIL-18 (2 hours IV infusion/wk) [13]. Lopus et al. examined DM1, a cytotoxic drug that binds and inhibits microtubule function, in a separate investigation. The researchers established the use of antibody-DM1 conjugates in cancer treatment. One example of an antibody-drug combination that has been created is the monoclonal antibody trastuzumab (Herceptin) in combination with trastuzumab emtansine (T-DM1). Trastuzumab emtansine was recently approved by the FDA as a breast cancer treatment. T-DM1 inhibits the overexpression of the epidermal growth factor receptor 2 (HER2) in aggressive breast cancer. Through its interactions with DM1 and microtubules, trastuzumab emtansine destroys cancer cells.

Delivering chemical substances that block DNA into the nuclei of cancer cells is the most effective way to kill tumor cells. The main challenge to this kind of tailored medication delivery is preventing active species from accessing endosomal or lysosomal vesicles [7]. Sui et al. described two ways to transport medicines into the nucleus. Indirect nuclear targeting is one approach that allows for complete sequestration of nuclear DNA by permitting significant amounts of drug molecules to be subsequently absorbed into the cytoplasm. By using nanocarriers to transport compounds over the cell membrane and into the cytoplasm, the second approach offers direct nuclear targeting. The active molecules are then released when the molecules eventually assemble in the nucleus.

3. MATERIALS AND METHODS

The primary barrier to nuclear drug delivery to mammalian cells is the plasma membrane, which obstructs large, charged hydrophilic molecules. Large nanocarriers can enter cells through a variety of endocytosis mechanisms. Geometry and other physical properties of the nanocarrier may have an impact on phagosome development. There are various forms of pinocytosis, including clathrin-mediated endocytosis (CME), caveolin-mediated endocytosis, clathrin and caveolin-independent endocytosis, and micropinocytosis. These studies highlight how crucial it is to consider the form and charge of particle delivery systems in order to get over the main obstacle of nuclear medication delivery. The ability of eukaryotes to have many cells enables compartmentalized architecture, which controls the differentiation of cells. The nuclear envelope, which encloses the nucleus, keeps the cytoplasm apart from the nucleoplasm and genetic material. Molecular exchange is facilitated by the nuclear pore complex (NPC), a component of the nuclear envelope [50]. The cytoplasmic ring, nuclear, and central channel of NPC are formed by 50 distinct proteins known as

nucleoporins. In a bidirectional fashion, individual NPC move about 1000 proteins per second [8]. Targeting signals are used to move molecules with a diameter of 9 nm or greater than 45 KDa into or out of the nucleus. On the other hand, passive diffusion allows tiny molecules to flow through the NPC. The entrance of particles larger than 100 nm has been reported in several papers, which is surprising. As a result, opinions on the specific mechanics of transfer via the NPC are divided[14].

It appears that more than 2100 clinical trials for gene therapy have been conducted and approved thus far. Gene therapy offers a potent and cutting-edge method of treating cancer in contrast to traditional chemotherapy, which is quite dangerous because of its lack of specificity. By delivering functional genes or genetic materials into the patient's cells at the molecular level, gene therapy corrects or replaces damaged genes. Malignant cells have mutations in genes like bax, and other oncogenes. These sequences work in a variety of ways once therapeutic genes are inserted into cells, such as by silencing, up- or down-regulating, repairing, or altering the particular target genes. Suicide genes can result in cell death and/or tumor necrosis. Gene silencing inhibits cell growth and tumor regression. Gene alteration may result in an increase in response to other combination therapies, such as immunotherapy, chemotherapy, or radiation[9].

The disease-causing viral gene part must be removed and replaced with therapeutic genes in order to use the virus as a vector. The therapeutic gene that generates the viral vector is one of the remaining non-pathogenic components of virus carriers. Linear double-stranded (ds) DNA is present in naked viruses known as adenoviruses (Ads). Ads are a particularly effective treatment for glioblastoma multiforme (GBM) because they may safely induce transduction with high transgene expression. However, significant toxicity and poor therapeutic efficacy following systemic dissemination restrict the use of advertisements in gene therapy. Many attempts have been made to increase treatment efficacy and decrease toxicity. In comparison to Ads, Yao et al. demonstrated that the PEGylated adenovirus vector increased tumor-selective transgenic expression. Ritonavir-containing treatment regimens may thereby enhance cancer cells' therapeutic exposure to anticancer medications, potentially enhancing chemotherapy's effectiveness while lowering the emergence of resistance.

4. RESULT AND DISCUSSION

Therefore, in order to maximize the use of the available financial and human resources, it is imperative to select patients who are having adherence problems at baseline. Additionally, it would be crucial to look into the characteristics of each patient, such as gender, as these could have an impact on the overall results of the interventions that are carried out.

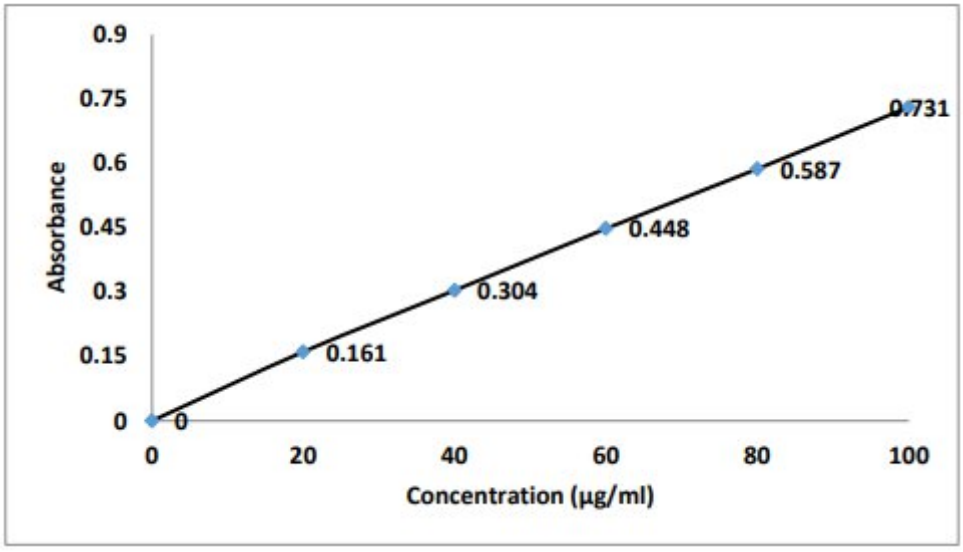

Figure 1: Standard graph of Etoposide in methanol

Similarly, HF-10, herpes simplex virus (HSV), and granulocyte-macrophage colony-stimulating factor (GM-CSF) all showed beneficial effects on ovarian cancer in mice. Retroviruses having ssRNA genomes are called lentiviruses. They have emerged as a promising vector in cancer gene therapy. Lentiviruses have a number of benefits over other viral systems, including low immunogenicity and the ability to transduce a variety of cells. Several attempts have been made to use lentivirus as a cancer gene therapy vector.

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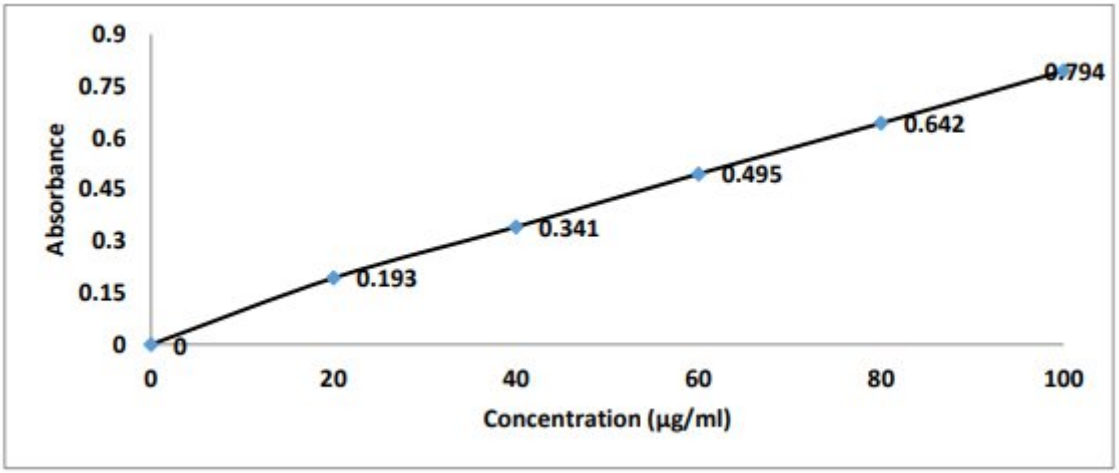

Figure 2: Standard graph of Etoposide in PBS

Protein phosphatase magnesium/manganese-dependent 1D (PPM1D) or high mobility group box 1 (HMGB1) were the targets of lentivirus-mediated RNA interference. These structures prevent the growth of bladder cancer.

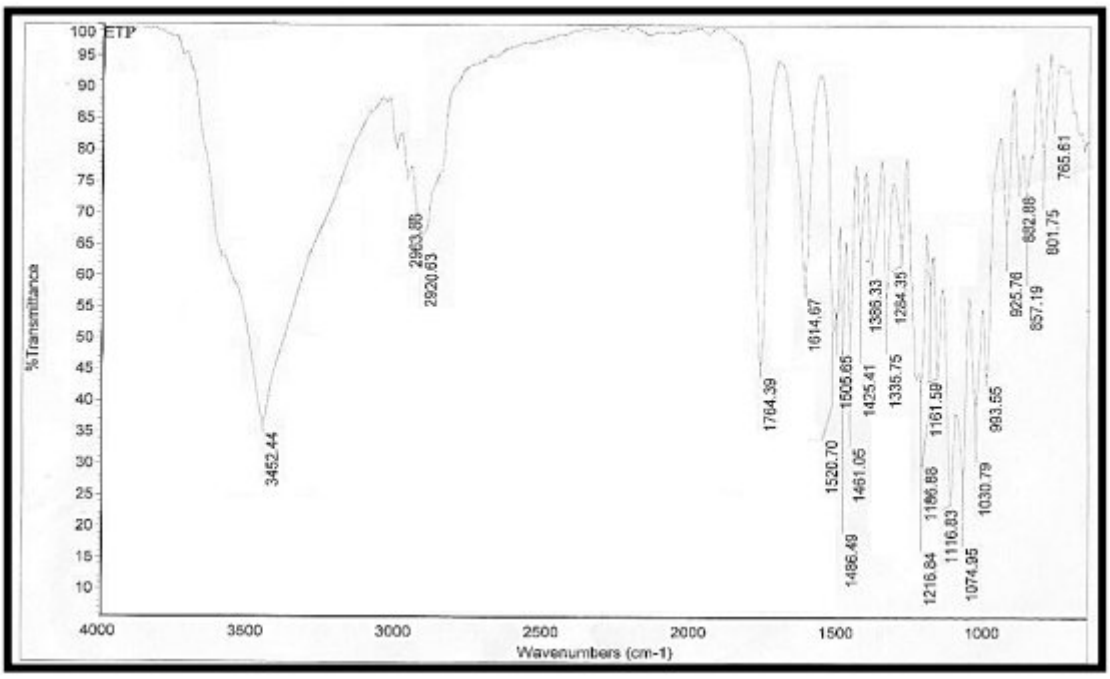

Figure 3: FTIR spectra of Etoposide

Many non-viral methods have been investigated for gene delivery, including the injection of bare DNA or physical methods such as electroporation, gene guns, hydrodynamic dispersion, nonoperation, and nanocarriers (nanoparticles and neutral or cationic liposomes). When it comes to large-scale manufacturing, minimal immunogenicity, and high transfection efficiencies, non-viral techniques are better than viral ones.

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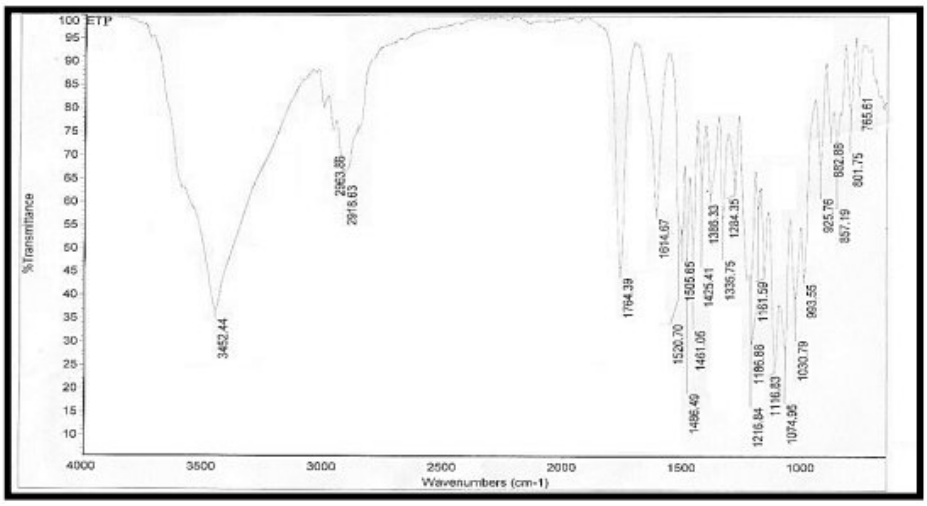

Figure 4: FTIR spectrum of Etoposide

Directly injecting free DNA into specific organs to induce gene expression is the most straightforward method of delivering therapeutic genes. This process is relatively cost-effective in terms of production and less immunogenic. However, its application is limited due to its low overall expression level. Notwithstanding their drawbacks, clinical experiments utilizing naked DNA plasmid delivery have shown some degree of success.

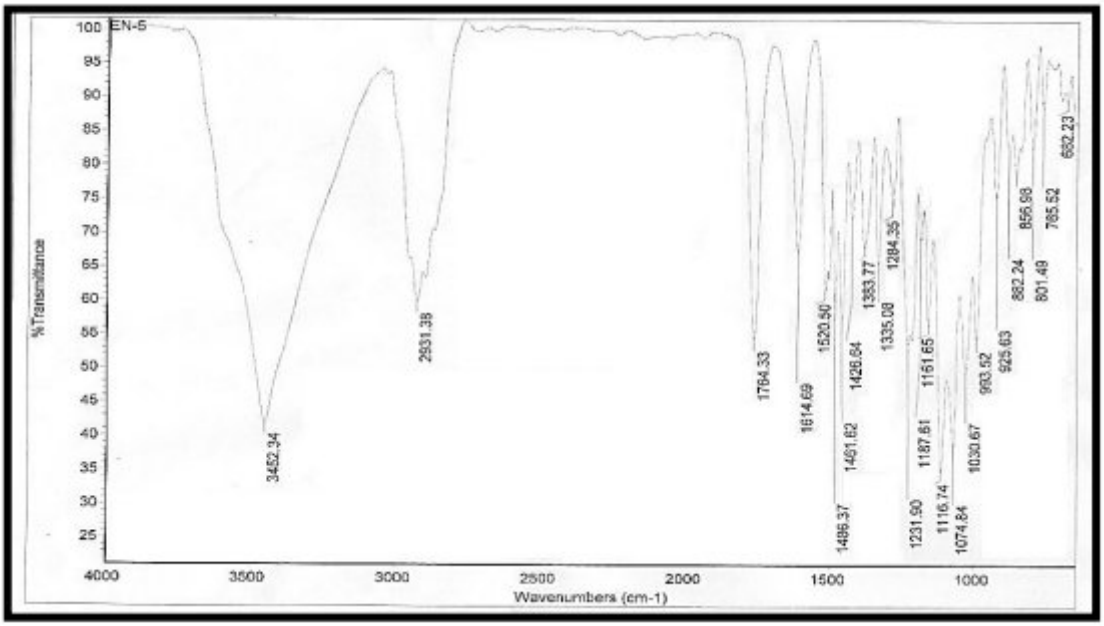

Figure 5: FTIR spectrum of Polymeric Etoposide

Localized gene expression, precise therapeutic gene delivery, and fewer side effects are just a few benefits of electroporation. Research has been done to make sure this approach is safe and tolerable for infectious illnesses and cancer. Another straightforward yet efficient non-viral gene delivery technique is hydrodynamic. A physical force that raises intravascular pressure is how it operates. This method is frequently used to deliver genes to animals. Transgenes can be safely and effectively delivered into mammalian cells using hydrodynamic gene delivery.

5. CONCLUSION

Cancer is rapidly rising to the top of the global death toll. Despite its typical cell toxicity, conventional chemotherapy has been the cornerstone of the fight against cancer. Due to their lack of specificity, conventional cancer treatments result in toxicities and severe side effects. It is necessary to develop new therapeutic strategies because cancer is so severe. Developing anticancer drugs that may be administered locally with little systemic harm is one of the biggest problems. Cell mass, extracellular matrix composition, and

angiogenic status are only a few of the variables that can change in an ebbing tumor. Preventative interventions have emerged as a result of recent advancements in drug delivery technology. New cell targeting techniques can be used to deliver novel chemo preventive drugs. These new methods concentrate on employing cutting-edge methods to cure cancer. Because they are less harmful to healthy cells, these innovative technologies offer new possibilities for cancer prevention and treatment that will soon be available in the clinic.

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