A REVIEW ON CARBON NANOTUBE: A NEW ERA IN CANCER DIAGNOSIS & THERAPY

By

Safi Parvez
18346026

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Student's Full Name & Signature:

Safi Parvez
18346026

Approval

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Supervised By:

_____

Full Name
Designation
School of Pharmacy
BRAC University

Approved By:

Program Director:

_____

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

_____

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Numerous treatments are now being used in clinical settings for cancer treatment. Over the past few years, a lot of progress has been made in the use of nanoparticles for biomedical applications, including its use in cancer treatment. One such example is carbon nanotubes (CNTs). Due to their unique physicochemical characteristics, CNTs have gained popularity as a tool for cancer treatment and diagnostics. With the ability to both identify malignant cells and deliver medications or other small therapeutic molecules to these cells; they are regarded as one of the most promising nanomaterials. CNTs have been investigated in nearly every cancer treatment technique and cancer diagnosis over the past few years, including drug administration, lymphatic targeted chemotherapy, thermal therapy, gene therapy, photodynamic therapy, photoacoustic imaging, fluorescence imaging, Raman imaging etc. Based on current research, this review article explains the function of carbon nanotubes in cancer treatment and diagnosis.

Keywords: Cancer; CNTs; Diagnostic; Imaging; Therapy; Drug-delivery.

Dedication

Dedicated to the innocent lives that cancer has taken

Acknowledgement

First of all, I want to give thanks and appreciation to God, the Almighty Allah, for granting me good health as well as the patience, dedication, and knowledge I needed to finish the thesis.

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List of Acronyms

CNTs	Carbon Nanotubes
WHO	World Health Organization
NHL	Non-Hodgkin Lymphoma
IARC	International Agency for Research on Cancer
SWCNT	Single-walled Carbon Nanotube
MWCNT	Multiwalled Carbon Nanotube
PET	Positron Emission Tomography
PAI	Photoacoustic Imaging
NIR	Near-infrared Region
TAT	Thermoacoustic Tomography
PAT	Photoacoustic Tomography
DOS	Density of States
MDR	Multidrug Resistant
DDS	Drug Delivery System
EPR	Enhanced Permeability and Retention
PDT	Photodynamic Therapy
PAA	Poly Acrylic Acid
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HPV	Human Papillomavirus
HP	Helicobacter Pylori

Chapter 1

Introduction

1.1 Cancer

A century ago, cancer was not as widespread; however, its prevalence has been drastically increasing in recent years. This is likely related to our modern lifestyle, habits, and longer life expectancies. Cancer is a condition with distinct characteristics. Simply cancer is defined as uncontrolled cell growth. It can form in any organ or tissue of the body and is composed of cellular organelles that have already lost their ability to stop growing.

Cancer, according to the World Health Organization (WHO), is a wide category of conditions that can begin in almost any organ or part of the body when abnormal cells divide uncontrollably, invade neighbouring regions of the body, and/or spread to other organs. The worldwide cancer burden keeps rising, putting enormous physical, psychological, and economic pressure on people, families, societies, and healthcare systems. Several healthcare systems in emerging and underdeveloped nations are unprepared to handle this burden, and the vast majority of cancer patients globally do not have access to timely, high-quality diagnosis and treatment. Men are more prone than women to develop lung, prostate, colorectal, stomach, and liver cancers and women are more prone to acquire breast, colorectal, lung, cervical, and thyroid cancers. (*Cancer*, n.d.).

1.2 Types of Cancer

Based on tissue affected:

- Carcinoma: Cells that cover both inner and outer body parts, such as those in lung, breast, and colon cancer, are known as carcinomas.
- Sarcoma: Sarcomas are distinguished by the presence of cells in bones, muscles, fat, connective tissue, cartilage, and other supporting tissues.
- Lymphoma: Lymphomas are termed as malignancies which start in the lymph nodes and immune system organs.
- Myeloma: Myelomas are cancers that start in the bone marrow's plasma cells. Some of the proteins contained in blood are produced by plasma cells.

- Leukaemia: Cancers called leukaemia's arise in the bone marrow and frequently start building up in the circulation.
- Adenoma: Adenomas are cancerous tumours that develop in the thyroid, adrenal gland, pituitary gland, and other glandular organs.

Based on organ affected: Depending on the tissue damage, we can identify a few additional forms of cancer. Lung cancer, liver cancer, colon cancer, stomach cancer, cervical cancer, bladder cancer, esophageal cancer, Non-Hodgkin lymphoma (NHL), nasopharyngeal cancer, Sarcoma Kaposi, lip cancer, oral cavity cancer, etc. are a few examples of cancers that impact organ. (Nain et al., 2015).

1.3 Aetiology

In several Asian nations, including Japan and Korea, cancer seems to have become the primary cause of death. It is also becoming a severe health hazard in several Asian nations. Lung, breast, colon, and rectum tumors are most frequently identified in Asia, and lung, stomach, and liver cancers cause the highest mortality. In Asia, there were over 3 million new cancer cases and over 2 million cancer deaths in 2000, and estimates indicate that if current preventive and care practices are not improved, the number of new cases of cancer in Asia would rise to 7.1 million by the year 2020. (Park et al., 2008).

There are several factors that might lead to cancer in various body regions, such as smoking tobacco (which accounts for 22% of fatalities), poor nutrition, overweight, inactivity, heavy alcohol intake, and other exposure to ionizing radiation, environmental toxins, and infection (which accounts for 10% of deaths). Approximately 15% of cancer cases globally are brought on by disorders such as Helicobacter Pylori (HP), Hepatitis B (HBV), Hepatitis C (HCV), Human Papillomavirus (HPV), Epstein-Barr virus, and HIV. These elements have altered the genes, at least in part. 5-10% of cancer cases are also brought on by inherited genetic abnormalities from the patient's parents. (Saini A, Kumar M, 2020)

Three types of external agents—genetic factors, environmental variables, and agents we consume—combine to produce cancer. Which are:

1. Chemical Carcinogens: These include substances like arsenic in drinking water, nitrosamines in food, asbestos, cadmium, benzene, benzidine nickel, and vinyl chloride, as well as over 60 other substances that are known to cause cancer.

2. Physical Carcinogens: The examples of physical carcinogens are ionizing radiation from sources such as radon, sunlight's ultraviolet rays, uranium, and sources that release alpha, gamma, beta, and X-rays.
3. Biological Carcinogens: Diseases with specific viruses, bacteria, or parasites, including HP, kaposi's sarcoma-associated herpesvirus, HBV and HCV, Markel cell polyomavirus, and HPV. (Saini A, Kumar M, 2020)

There are some factors responsible for causing cancer. The factors are given below-

Table 1: Cancer-causing factors (Nain et al., 2015)

Name of cancer	**Causes**
1. Melanoma	UV radiation
2. Bone cancer	Radium, Pesticides
3. Brain cancer	Ionizing radiation, Chromium, Methylene Chloride
4. Prostate cancer	Aromatic Amines, Methyl Bromide, Agent Orange, Organ Chloride Pesticides, Pesticides, PAHs, Solvents
5. Liver cancer	Aflatoxin B1, Ethyl Alcohol, Androgens, N-nitrosodimethylamine, Arsenic, Hydrocarbons, PCBs, Captafol, Trichloroethylene, Thorium dioxide, Vinyl Chloride
6. Thyroid cancer	Ethylene Thiourea, Ionizing Radiation
7. Leukemia’s	Agent Orange, Ionizing Radiation, Carbon tetrachloride, Benzene, Metal dusts, Secondhand smoke, Chlorinated solvents, Trichloroethylene
8. Colorectal cancer	Alachlor, Chlorination by-products, 1,1-dichloroethane, Solvents, Aromatic Amines, Ionizing Radiation,

1.4 Risk Factors

1.4.1 Life Style

Large regional variations in the incidence of cancer may have genetic, behavioral, or environmental causes. For instance, it has been suggested that the main cause of the modern approaches in breast, colon, rectum, and prostate cancer in Asian countries is really the adjustment of the "western" style of living, which is a mixture of reduced parity, late bearing children, early menstrual irregularity, relatively high calorie or fat consumption, and physically inactive lifestyle or modest life pattern.

- Alcohol consumption and smoking tobacco: The greatest lifestyle-related, preventable relative risk for cancer is tobacco. Depending cancer location and gender, smoking tends to have various impacts on cancer development. Smoking had been a significant risk factor for developing lung cancer. Smoking does not appear to have a definite impact on other malignancies, though. Smoking was mentioned as a potential risk factor for breast cancer, although the danger of colon and liver cancer wasn't really supported by enough data. (Yamaguchi et al., 2000). Again, overindulgence in alcohol consumption is also another major cancer-causing risk factor. According to a meta-analysis conducted in Japan, even people who consume 46 g/day used to have a greater risk of developing colorectal cancer and breast cancer. (Mizoue et al., 2006). In addition, alongside cigarette smoking and alcohol intake, the International Agency for Research on Cancer (IARC) recognized betel nut chewing, which is highly popular in South-East Asia, as a human carcinogen. It also develops esophageal squamous cell carcinoma according to a Taiwanese investigation. (Wu et al., 2006).
- Physical inactivity: Numerous studies have connected a lack of physical exercise to a higher risk of breast and colon cancer. A Japanese study found that individuals who engage in a substantial amount of physical activity have a lower chance of getting female breast cancer. (Hirose et al., 2003).
- Dietary factors: Numerous studies have looked into the connection between diet and nutrition and the chance of developing cancer. Recent studies have focused more attention on certain Asian diets that could have preventive effects on cancer risk. First of all, there was a high overall calorie and fat consumption. It was demonstrated in such a series of epidemiological research studies conducted in Asia that consuming red meat and animal fat enhanced the risk of acquiring colorectal and breast cancer. (Seow et al.,

2002). Secondly, some studies revealed that poor intake of vegetables and fruits is linked to a higher risk of developing cancer in Asian nations, despite some discrepancies being discovered. According to a research study conducted in India, men who consume more vegetables and fruits had a lower chance of developing prostate cancer. (Sunny, 2005). Moreover, gastric cancer risk as well as the incidence of HP infections are known to rise with increased salt and salty food consumption. In addition to their impact upon HP infections, salt and salted foods work together to encourage the growth of gastric cancer. (Monographs & 1992, n.d.).

1.4.2 Environmental Carcinogens

The quality of air has gotten much worse in Asian nations because of rapid industrial growth, and air pollution has emerged as a problem. For instance, compared to western countries, many cities have higher amounts of polycyclic aromatic hydrocarbons (PAHs) which is a proven health carcinogen. This also increases the risk of lung cancer. According to studies conducted in northeast China, exposure to smoky outside surroundings, continuous use of coal burners, and high inside air pollution are all associated with a two-fold increased risk of lung cancer. (Xu et al., 1989). Lung cancer risk was shown to be increased when coal was used for both cooking and heating purposes. Again, lung cancer and bladder cancer are also linked to the exposure to arsenic according to data from a Taiwanese region. Mining and smelting employees subjected to inorganic arsenic in China had a threefold greater chance of developing lung cancer. (Wu Williams et al., 1990). Furthermore, other recognized environmental variables that increase the risk of developing lung cancer include radon and asbestos.

1.4.3 Factors Related to Reproduction

Premature menarche, delayed menopause, reduced lifetime breastfeeding length, and oral contraceptive usage are all recognized to raise the chance of breast cancer. In several Asian nations, epidemiological research has shown similar findings about such potential factors. (Park et al., 2008; Yoo et al., 1992; Zheng et al., 2000). Reproductive variables may also be linked to a higher risk of colorectal cancer, according to certain research. These reproductive parameters include the age at menopause, the timing of menarche, the regularity of menstruation, the number of abortions, and the first pregnancy. It was proposed that hepatic functionality and the production of bile juice are two ways in which reproduction activities may influence the malignancy in the big bowl. (Tamakoshi et al., 2004).

1.4.4 Infection-causing Agents

Significant risk factors for the growth of gastric, liver, and uterine cervical cancer include HBV, HCV, HP and HPV. HBV and HCV carriers have a 20-fold and a 25-fold increased risk of developing liver cancer, respectively, compared to non-carriers. (*Asian Pacific J. Cancer Prev.*, n.d.). Furthermore, it has been proposed that liver flukes like Clonorchis Sinensis (CS) and Opisthorchis viverrini (OV) are potential factors for liver cancer, including cholangiocarcinoma (CCA) and hepatocellular carcinoma. It is well recognized that the chronic inflammation brought on by a persistent infestation plays a part in how liver flukes contribute to the development of cancer. Asia has a significant HPV prevalence, particularly in India and China. (Franceschi et al., 2006).

1.5 Prevalence

The incidence of a specific cancer refers to the proportion of people in a defined group who had that form of cancer at some point in the past and were still living at the end of that year. often presented as a number and a percentage per 100,000 people at the end of 2008, there were about 29 million people alive who had received a cancer diagnosis within the preceding five years. Were mostly women (5.2 million) after receiving a breast cancer diagnosis, followed by men and women (3.3 million) after receiving a colorectal cancer diagnosis, and then males after receiving a prostate cancer diagnosis (3.2 million). Research outlines the key outcomes and briefly discusses the data sources and methodologies used in creating the International Agency for Research on Cancer (IARC) GLOBOCAN cancer data for the period of 2020. The results are as follows:

Table 2: Leading types of cancer in terms of new cases (incidence) and deaths (mortality) by males worldwide in 2020. (Ferlay et al., 2021)

	Incidence			**Mortality**	
	First	**Second**		**First**	**Second**
World	Lung	Prostate		Lung	Liver
Africa	Prostate	Liver		Prostate	Liver
Americas	Prostate	Non-melanoma skin		Lung	Prostate
Asia	Lung	Stomach		Lung	Liver
Europe	Prostate	Lung		Lung	Prostate

Oceania	Non-melanoma skin	Prostate		Lung	Prostate

Table 3: Leading types of cancer in terms of new cases (incidence) and deaths (mortality) by females worldwide 2020. (Ferlay et al., 2021).

	Incidence			**Mortality**	
	First	**Second**		**First**	**Second**
World	Breast	Lung		Breast	Lung
Africa	Breast	Cervix uteri		Breast	Cervix uteri
Americas	Breast	Non-melanoma skin		Lung	Breast
Asia	Breast	Lung		Lung	Breast
Europe	Breast	Lung		Breast	Lung
Oceania	Non-melanoma skin	Breast		Lung	Breast

1.6 Current Cancer Diagnostic Method

Cancer diagnosis is essential for successful treatment. Cancer in its early detection focuses on identifying symptomatic individuals as soon as possible so that they may receive the best available treatments. If cancer care is neglected or inadequate, there is a reduced likelihood of survival, more therapeutic complications, and increased treatment expenses. By treating patients at the earliest stage, early detection enhances disease outcomes and is thus a vital public health approach in all contexts. Early cancer detection methods that succeed could save lives and lower the financial, social, and monetary costs of cancer treatment. (*Promoting Cancer Early Diagnosis*, n.d.). The following section discusses a few of the tests that are frequently performed to help with a cancer diagnosis.

1.6.1 Lab Tests

A procedure in which a sample of blood, urine, tissue and other bodily fluid is examined to learn about the health of the patient is called a laboratory test. Certain laboratory tests offer accurate and trustworthy details concerning particular health issues. Some tests offer more

comprehensive data that enables doctors to recognize or rule out potential health issues. The following list includes categories for some typical laboratory tests used in cancer treatment. (*Understanding Laboratory Tests Fact Sheet - NCI*, n.d.).

- **Complete blood count (CBC):** It measures the quantity of various blood cell types, such as platelets, white blood cells, and red blood cells, in a sample of blood. The hematocrit, the proportion of red blood cells to total blood volume, the size of red blood cells, and the quantity of hemoglobin in red blood cells are all also measured by this test. It is used to diagnose cancer, especially leukemias, and to follow patients before and after therapy.
- **Cancer gene mutation testing:** It assesses the presence or lack of particular hereditary gene mutations that have been linked to the growth of cancer. For instance, testing for BRCA1 and BRCA2 gene mutations, which are linked to the growth of breast, ovarian, as well as other cancers. It is used to determine the risk of cancer.
- **Cytogenetic analysis:** It is used to diagnose illnesses and determine the best course of therapy because it examines changes in the amount or structure of chromosomes in a patient's white blood cells or bone marrow cells.
- **Blood chemistry test:** It monitors the levels of certain compounds, including metabolites, electrolytes, lipids, and proteins, including enzymes, which are discharged into the bloodstream by the body's tissues and organs. It comprises tests for creatinine and blood urea nitrogen (BUN). It is utilized for patient diagnosis, therapy monitoring, and follow-up. Certain substances' high or low concentrations might signal illness or represent unwanted side effects of therapy.
- **Immunophenotyping:** Based on the kinds of antigens found on the cell surface, it recognizes cells. Lymphomas, leukemias, myeloproliferative diseases and myelodysplastic syndromes are just a few examples of the hematologic conditions it is used to diagnose, stage, and monitor. It may be carried out on a variety of body fluids or biopsy tissue samples, although it is most frequently carried out on blood or bone marrow samples.
- **Tumor marker tests:** In tissue, blood, as well as other biological fluids, several tests evaluate the presence, concentrations, or activity of particular proteins or genes that may indicate the existence of malignancy or other benign (noncancerous) disorders. A medication that targets a tumor marker may be used to treat a tumor that has higher than normal levels of that marker. Several tumor marker tests use DNA analysis to search

for particular gene alterations that may only be present in cancerous tissues and not in healthy ones. Multigene tests, also known as multiparameter gene expression assays, are another type of tumor marker test that examines the expression of a selected collection of genes in tumor samples. Prognosis and treatment planning involve these tests. It is utilized in the diagnosis, selection of the best course of action, evaluation of the therapeutic response, and surveillance for the return of cancer.

- **Sputum culture:** it determines whether there are any aberrant cells in sputum (mucus and other material expelled from the lungs as a result of coughing). Lung cancer is diagnosed using it.
- **Urine cytology:** It detects diseases by assessing the presence of aberrant cells discharged from the urinary system into urine. It is used to identify and diagnose bladder cancer and other urothelial malignancies, as well as to follow individuals for cancer recurrence.
- **Urinalysis:** It determines the color of urine as well as its contents, which include protein, sugar, white blood cells and red blood cells. Used to detect and diagnose kidney and urothelial malignancies.

1.6.2 Imaging Tests

Imaging tests provide images of several inner body regions that enable the physician to detect whether such a tumor exists. There are various techniques to create these images (*How Cancer Is Diagnosed - NCI*, n.d.):

- **MRI:** A strong magnet and radio waves are used in an MRI to take slices of the body as photographs. Slices of the body are utilized to produce finely detailed pictures that can differentiate between healthy and diseased tissue. Before or during the MRI test, patients could occasionally have such a special dye injected through the vein. Tumors may seem brighter on the images when using this dye, which is referred to as a contrast agent.
- **CT scan:** A CT scan takes multiple images of the organs from multiple angles using an x-ray machine connected to a computer. These images are used to produce in-depth 3-D models of the body's interior that aid in cancer diagnosis.
- **Ultrasound:** People cannot hear the high-energy sound waves used in an ultrasound examination. The body's internal tissues reflect the sound waves. These echoes are used by a computer to produce images of specific regions inside your body. A sonogram is

a term given to this image. Patient will lay on a table during an ultrasound examination as a technician carefully passes a transducer over the skin of the body portion being examined. Warm gel coating the transducer allows it to slide over the skin.

- **Bone scan:** Nuclear scans known as "bone scans" are used to look for abnormal bone growth or injury. They can be utilized to identify tumors that have spread to the bones or bone cancer. It is also called a metastatic bone tumor.
- **X-rays:** Low radiation dosages are used by X-rays to provide images of the inside organs. Individuals will be positioned by an x-ray technician, who will also point the x-ray beam in the right direction for the body. Patients will need to remain completely still throughout the session, and they may have to hold their breathing for a little period of time.
- **Biopsy:** To diagnose cancer, physicians often perform a biopsy. A biopsy is a technique where a tissue sample is removed by the doctor. To determine whether the tissue is cancerous, a pathologist examines it using a microscope and does other tests. There are several ways to obtain the biopsy sample.
    - **Using a needle:** A needle is used by the physician to remove tissue or fluid. This technique is applied for certain prostate, breast, and liver biopsies as well as bone marrow aspirations and spinal taps.
    - **Endoscopy:** A tiny, illuminated tube known as an endoscope is used by the doctor during an endoscopy to view specific locations within the body. Endoscopes are inserted into the mouth or other natural bodily openings. Through the endoscope, the physician will remove any cancerous tissue he finds during the examination along with part of the adjacent healthy tissue. Example includes: Colonoscopy, Bronchoscopy etc.
    - **Surgery:** During surgery, a surgeon eliminates a region of abnormal cells. Excisional or incisional surgery are both possible. The surgeon completely excises the region of abnormal cells while in an excisional biopsy. Frequently, part of the healthy tissue surrounding these cells is also cut away. A little portion of the abnormal region is excised during an incisional biopsy by the surgeon.

1.7 Current Treatments

There seem to be numerous cancer treatments available. The type of cancer the patients have and the stage along it is will determine the treatments that they receive. Some cancer patients

will only receive one treatment. However, the majority of patients have a combination of therapies, including surgery along with radiation therapy and chemotherapy. There are some available cancer treatments given below. (Nain et al., 2015)

- **Gene Therapy:** By introducing new genes into a diseased cell or the tissue around it, a novel therapy method called gene transfer can either kill the cancerous cell or stop it from spreading. A wide variety of genes and vectors are being employed in clinical trials with positive results because of the versatility of this therapy method.
- **Targeted Therapy:** A more recent type of cancer treatment called targeted therapy utilizes medicines or other chemicals to more specifically locate and kill cancer cells, typically with little harm to healthy cells. The use of targeted therapy in cancer treatment options is currently increasing.
- **Surgery:** In some circumstances, surgery may be used to detect, treat, or possibly assist prevent cancer. Most cancer patients will undergo some sort of surgery. When cancer has not progressed to other body parts, it frequently gives the best chance of recovery.
- **Chemotherapy:** Utilizing medications or drugs to treat cancer is known as chemotherapy (or "chemo"). Many individuals are afraid of getting chemotherapy. However, understanding chemotherapy, how it functions, and what to anticipate can frequently allay your concerns. Additionally, it may increase the patient's sensation of control throughout the cancer therapy.
- **Radiation Therapy:** High-energy particles or waves are used in radiation therapy to kill or damage cancer cells. Whether used alone or in combination with other treatments, it is among the most popular cancer treatments.
- **Immunotherapy:** Cancer patients who receive immunotherapy benefit from the immune system's assistance in fighting the disease. In essence, it is a form of cancer treatment that boosts the immune system of the patient to fight cancer.
- **Photodynamic Therapy:** A medication that is triggered by light is used in photodynamic treatment to kill cancer cells and other unhealthy cells. In order to cure cancer, a technique known as photodynamic therapy (PDT) employs special medications known as photosensitizing agents together with light. The medications only function after being "switched on" or activated by specific types of light.
- **Lasers in Cancer Treatment:** Blades (scalpels) can be replaced with lasers, which are extremely strong, focused beams of light, allowing high-accuracy surgical tasks, including the treatment of some tumors.

- **Hyperthermia:** The concept about using heat to treat cancer has been around for a while, but the outcomes of the first experiments were inconsistent. The use of hyperthermia against various cancers is being researched because of new instruments that enable more accurate administration of heat.
- **Stem Cell Transplant:** Patients who have had their stem cells destroyed by aggressive chemotherapy or radiation therapy can get stem cell transplants to replace the ones that were lost.
- **Biomarker:** Testing for biomarkers is a means to find genes, proteins, and other components (also known as tumor markers or biomarkers) that can reveal information about cancer. A doctor can select a cancer treatment with the aid of biomarker testing.

1.8 Carbon Nanotubes

To treat life-threatening illnesses like cancer, better disease diagnostics and cutting-edge medicines are necessary. In order to achieve these objectives, carbon nanomaterials have emerged as potential materials. As nanotechnology advanced, several nanomaterials were created and used in industry. Among the nanomaterials that have seen significant usage in this field recently is carbon nanotubes (CNTs). Iijima made the initial discovery of carbon nanotubes in 1991, which are composed of thin sheets of carbon with benzene rings that have been wrapped up into a continuous tubular structure. Along with graphite and diamond, fullerenes are the third allotropic carbon form. This unique structure is a member of the fullerene family. Laser ablation, electric arc discharge, and thermal or plasma-enhanced chemical vapor deposition (CVD) are the three main methods used to create CNTs. (Ji et al., 2010). They are becoming more and more popular due to their special characteristics. In biological applications, CNTs are much more dynamic than other nanomaterials, and they rank among the most promising nanocarriers in research. As innovative delivery mechanisms, CNTs have shown a clear possibility of overcoming biological barriers. As unique delivery methods, CNTs have proven a clear possibility of overcoming biological barriers. In contrast to quantum dots, which have mostly been used during cancer cell imaging, CNTs can be employed for thermal ablation and drug delivery. They can penetrate the cell, and this action is independent of the surface functional group and cell type. (Z. Chen et al., 2017).

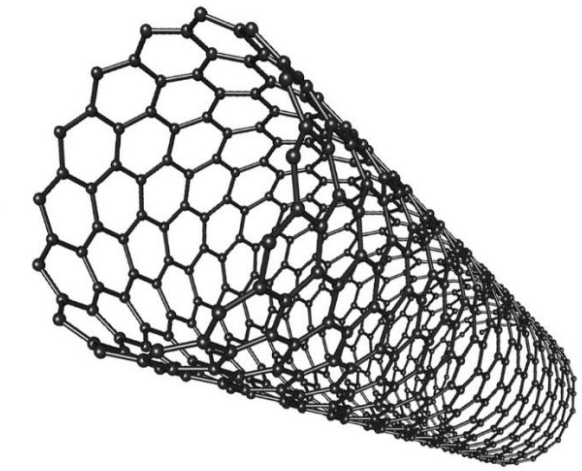

Figure 1: Carbon Nanotube (Chernova et al., 2017)

Generally, CNTs are divided into two categories: single-walled (SWCNT) and multi-walled (MWCNT). Depending upon the temperature at which they were created, SWCNTs are made up of a single cylindrical carbon layer with such a diameter that ranges from 0.4 to 22 nm. It has already been noted that a greater diameter results from a higher growing temperature. MWCNTs, in comparison, are typically constructed from many cylindrical carbon layers, with both the inner tubes' diameters ranging between 1-3 nm and the outer tubes' diameters ranging between 2-100 nm. The structure of the two types of CNTs differs from one another. In terms of SWCNTs, the structures are arranged in armchair, zigzag, chiral, or helical patterns. On contrary, the MWCNTs structure depending on how the graphite sheets are arranged can be separated into two categories. One is a structure resembling a "Russian doll," in which the graphite sheets are stacked one on top of the other, and the other is a model resembling parchment, where a single graphite sheet is wound around itself. (Madani et al., 2011).

Comparison between SWCNTs and MWCNTs-

1. SWCNTs should be utilized instead of MWCNTs if CNTs are necessary for electric transportation. This is due to the fact that MWCNTs are semiconducting, but SWCNTs can be both semiconducting and metallic.
2. SWCNTs are considered to be more effective in delivering drugs than MWCNTs. This is a result of the SWCNT's one-dimensional shape and effective drug-loading ability due to its extremely large surface area.

3. As a result of the improved permeability and retention effect, it has been found that an SWCNT-anticancer drug complex has a substantially longer blood circulation duration than the anticancer drug alone, which can result in a more extended and sustained uptake of the medication by tumor cells. However, it is known that MWCNTs are superior to SWCNTs for the thermal treatment of cancer. This is because the MWCNTs release a significant amount of vibrational energy after being exposed to near-infrared light. When this energy is released inside a tissue, it causes localized heating that can be used to kill cancer cells. (Madani et al., 2011).

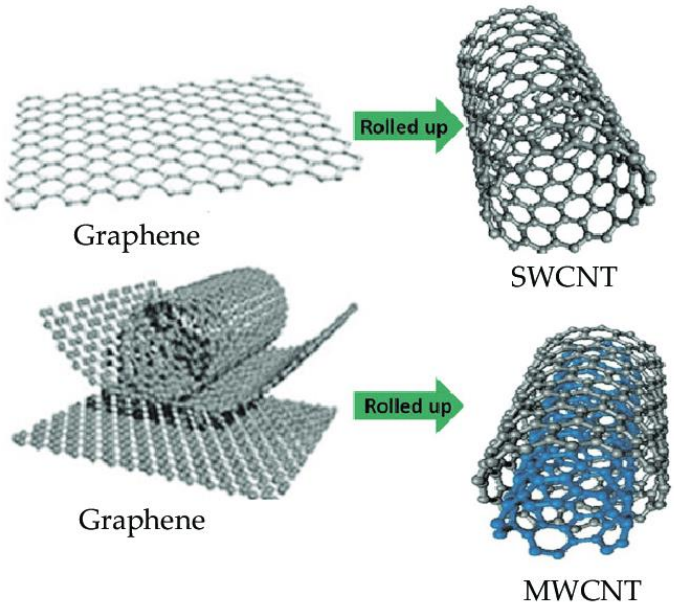

Figure 2: Schematic diagram of SWCNT and MWCNT (Nurazzi et al., 2021)

1.9 CNTs are Potential Option

Surgery, chemotherapy, and/or radiation therapy are the mainstays of modern cancer treatments. Since tumor cells are more vulnerable to the effects of chemotherapy and radiation, their goal is to destroy them. The well-known side effects, however, significantly limit their actual advantages and narrow the pool of applicants. Nanotechnology offers creative and exciting alternatives to current methods of tumor treatment. (Seeta Rama Raju et al., 2015). In the past 20 years, Carbon Nanotubes (CNTs) have drawn a great deal of attention and interest due to their distinctive mechanical characteristics and highly intriguing electrical and thermal conductivity values. Additionally, the ability to functionalize their surface with a variety of bio/chemical species opens the door for a wide range of therapeutic and drug usage. These make them unique among the most recent methods of cancer "theranostic" treatment, which

combines the diagnosis and treatments in a single nanostructure. (Lim et al., 2015; Marchesan et al., 2015).

Due to their size and inability to exit cancer cells because of an insufficient lymphatic system, nanoparticles' unique property in the fight against cancer is their capacity to invade tumor tissues. This characteristic, known as "Enhanced Permeability and Retention" (EPR), emphasizes the need for properly regulated and designed nanoparticle dimensions. (Seeta Rama Raju et al., 2015). The main drivers of the recent exponential growth in the area of study in cancer nanomedicine are the unusual resistance of cancerous cells to conventional anticancer treatments (such as chemotherapy, radiation, as well as surgery), in addition to unfavorable reactions to these treatments. Many different types of nanomaterials can serve as carriers for chemotherapeutic drugs when appropriately created, and cutting-edge functionalization enable them to target cancer tissues specifically. Additionally, combination therapies involving nanoparticles are also the focus of recent studies. However, CNTs are capable of more than only drug delivery in the fight against cancer. Customized CNTs can improve drug cytotoxicity and serve as effective adjunct Contrast Agents (CA) for a variety of imaging methods. Additionally, they can be used to carry out thermal ablation, find specific antigens or reactive oxygen species (ROS), as well as tumor indicators. CNTs can be functionalized in one of two ways: covalently or non-covalently. Both have advantages and disadvantages, with the covalent one having strong binding but altered electrical properties and the non-covalent one having very weak binding but preserved electrical qualities. Due to these factors, the appropriate functionalization technique must be determined based on the application. (Sanginario et al., n.d.).

1.10 Aim and Objectives

The purpose of this review of the literature is to emphasize the significance of using carbon nanotubes for cancer treatment and diagnosis. Other goals include advancing research and raising interest so that researchers may focus more on creating cancer treatments based on carbon nanotubes utilizing the nanotechnologies outlined under this review article.

Chapter 2

Research Methodology

A thorough literature research was carried out to gather relevant information for this review study. A number of trustworthy sources, including peer-reviewed journals and an online scholarly database, were used to gather the information. Here is a list of a few of the several databases that have been searched for this study.

- Journal Database
- Newspaper Database
- Professional website
- Library Catalogue

In order to gather as much essential information as possible regarding the use of carbon nanotubes in cancer diagnosis and treatment, a thorough search of several journals, review articles and research papers from official websites and research databases was carried out. Utilizing well-known and reliable sources including PubMed, SCOPUS, Google Scholar, and ScienceDirect, the data for this review study was collected. Relevant papers were gathered using appropriate important keywords, such as cancer, nanomaterial, carbon nanotube, and use of nanotechnology in cancer. Around 107 articles have been assessed based on the title and keyword content. Then, 58 papers were reduced after reading the abstracts. The 49 papers that made up this review research were carefully selected and examined. Mendeley software was used for accurate and fair referencing in order to show respect for the writer's original works.

Chapter 3

Application of Carbon Nanotubes (CNTs) in Cancer Diagnosis

Early screening and diagnosis are crucial because only radical removal of the tumor at an early stage can cure the condition. The majority of tumors, however, are asymptomatic in the early stages. Additionally, traditional clinical cancer imaging methods including X-ray, CT, and MRI lack the spatial resolution needed for early disease identification. Most early neoplastic illnesses lack recognizable morphologic alterations, making it easy for conventional imaging tools to miss them. Modifications in tissue biochemistry and metabolism are the basis for the very precise and sensitive imaging technology known as positron emission tomography (PET). It is the most useful tool we currently have for locating early-stage molecular biology alterations, frequently prior to any morphologic alteration. (Ji et al., 2010). In recent years, research into the identification of biomarkers that could be used to diagnose cancer has been more active. Early screening and identification have become important for cancer therapy since drastic resection of the tumor is the sole treatment option for this illness while it is in its early stages. The majority of malignancies do not exhibit visible symptoms when they are in their early stages, and conventional clinical cancer imaging techniques do not have sufficient resolution for prognosis assessment or early diagnosis. Early cancer diagnosis is based on changes in tissue characteristics such as optical absorption, mechanical properties, and RF absorption. Finding novel methods for the early identification of cancer is crucial. Here, researchers offer a fresh perspective on the various diagnostic principles that have utilized nanotubes. Some cancer diagnostic approaches in its early stage based on carbon nanotubes are given below.

3.1 Photoacoustic Imaging

Photoacoustic imaging (PAI) is a contemporary imaging method that has been widely utilized in a variety of biomedical applications. The PAI theory is straightforward. A broadband ultrasonic emission is produced when a pulse laser interacts with an absorptiometric molecule with in biological sample, producing heat. This short-lived thermoelastic inflation can then be explored by an ultrasound microphone, and the detected signals were then used to create 2D or 3D images. When compared to conventional optical imaging techniques, PAI has the advantage of offering greater spatial resolution and imaging of deeper layers of the skin. It has become vital to regulate external photoacoustic contrast-media. As contrast-mediums in PAI, a variety

of nanomaterials have been used, and these materials have a strong ability to absorb light in the near-infrared region (NIR). MWNTs and SWNTs have been employed as a photothermal agent because of their high NIR absorbance. (Z. Chen et al., 2017). Additionally, the solid NIR absorbency of nanotubes make them ideal contrast-mediums for PAI. In thermoacoustic tomography (TAT) and photoacoustic tomography (PAT), SWNTs can provide signals that are amplified more than twofold and more than sixfold, respectively, in comparison to controls. SWNTs can be used in the PAI as the optimum contrast-mediums since they can produce the most signal when compared to certain other carbon materials, fullerenes, and graphitic microparticles. (Pramanik, Swierczewska, et al., 2009).

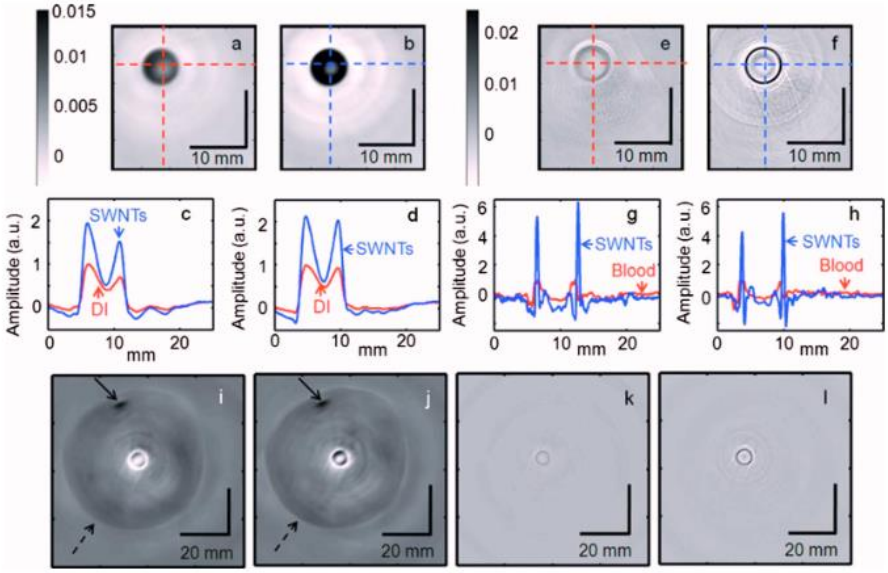

Figure 3: Cross-sectional TAT and PAT image of different vials containing DI water and 1-mg/ml SWNTs and their comparisons. *(Pramanik, Swierczewska, et al., 2009).*

To increase SWNTs' absorbance in the NIR regions, gold-coated layers or biocompatible molecules must be added. Some researchers have created "golden nanotubes" (GNTs) because gold plating can boost the photoacoustic signal that SWNTs naturally produce. Additionally, to increase the optical density, various NIR dyes, such as indocyanine green (IGG) molecules, can be placed on PEGylated SWNTs, resulting in the existence of multiplexed PAI probes. As a result, CNTs with high NIR absorbance have emerged as a promising contrast agent for PAI. CNTs are a universal nanoplatform because they may be paired with various absorptivity nanomaterials to increase or multiplex PAI in addition to using their inherent optical absorbance. Currently, the bulk of CNTs-based PAI probes rely on SWNTs, while MWNTs could also be useful for this imaging method. (Z. Chen et al., 2017).

3.2 Fluorescence Imaging

For the purposes of medical diagnostics, fluorescence imaging (FI) is essential. However, the depth of penetration has restricted their further use in fluorescence imaging. Several researchers have been trying to develop and enhance fluorescence probes continuously in order to address this issue. Only a small fraction of synthesized SWNTs can fluoresce when stimulated by laser light; the majority of SWNTs, on the other hand, do not fluoresce when excited by laser light, and these non-fluorescent SWNTs are dark field images. Therefore, the majority of nanotubes administered into animals can result in a large drop after polarization-purified SWNTs are administered. Density of states (DOS) can be well characterized by Van Hoff singularities (VHSs), which have constrained, narrow energy bands having high DOS. Every semiconducting SWNT has an energy band gap of around 1 eV, and this property ensures that fluorescence in the NIR-II area occurs in response to stimulation in the NIR-I region. (Z. Chen et al., 2017). A well-functionalized SWNTs formulation was created by Robinson et al.; this preparation seems to have a half-life of 30 hours in bloodstream in vivo, accumulating more than 30% of the inject dose (% ID/g) of the medication. For the first time, fluorescent signals in cancers and other organs have been observed using high fluorescence video rate imaging and principal component analysis (PCA). After a 20 second injection, they could clearly observe fluorescent signals inside the tumor, and the signals might last for up to 72 hours.

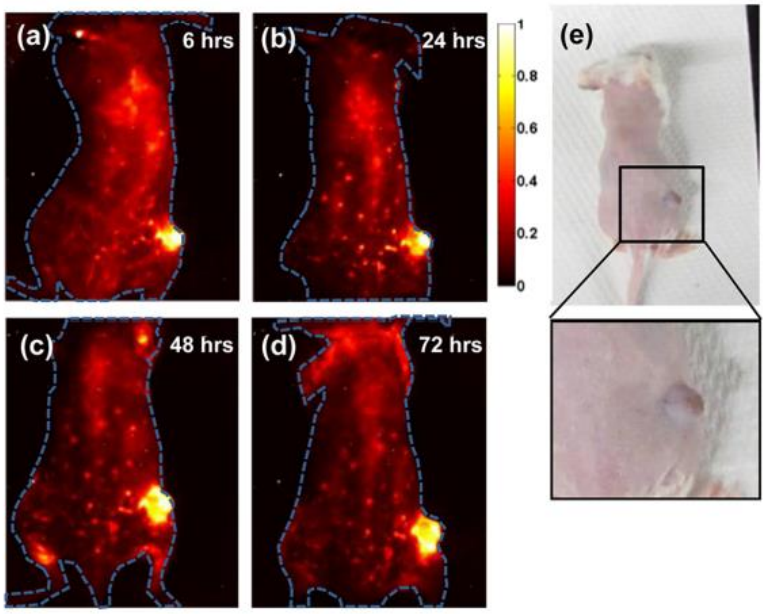

Figure 4: NIR-II imaging of xenograft 4T1 tumor with high uptake of SWNTs. (Liu, Li, et al., 2008).

Additionally, by employing technology for 3D reconstruction of NIR-II fluorescence data, they have also observed the colocalization of tumor vasculatures and SWNTs within the tumor. This finding suggested that nanotube accumulation in tumors may be significantly mediated by the effect of permeability and retention (EPR). (Robinson et al., 2012). As a result, the SWNTs-based NIR-II FI offers tremendous potential for use in biological diagnostics, and its unique benefits over other imaging methods have been demonstrated. Additionally, because SWNTs differ in their excitation and emission wavelengths, they may be an advantageous material for multicolor NIR-II fluorescence imaging.

3.3 Raman Imaging

The photon scattering mechanism known as Raman scattering involves the emission of photons with altered wavelengths in response to light stimulation. Since surface-enhanced Raman scattering (SERS) is not a process used to augment the intrinsic Raman scattering signals of molecules, these signals are often quite low. The radical breathing mode (RBM, 100–300 cm1) and tangential G band (1580 cm1) are two Raman peaks that SWNTs have. These Raman peaks are consistent with the radical and tangential oscillations of carbon atoms, respectively. The sharp and narrow Raman peaks of SWCNTs make it very simple to identify the autofluorescence background. The NIR range is a transparent window for in vivo imaging because the Raman excitation and scattering photons of SWCNTs may reach there. With isotopically engineered SWCNTs, Dai and colleagues have discovered several Raman imaging techniques for live cells. In this study, SWCNTs with various isotope (12C and/or 13C) compositions—each of which has discrete Raman G band peaks—have been investigated, and several cancer cells with various surface receptors have been used to target receptors specifically. The ability of each targeted ligand to recognize its individual receptor has enabled multiplexed multicolor Raman imaging of cells. Multiplexed Raman detection of several proteins may be demonstrated when pure 12C- and 13C-SWCNTs are attached by various antibodies. (Z. Chen et al., 2017).

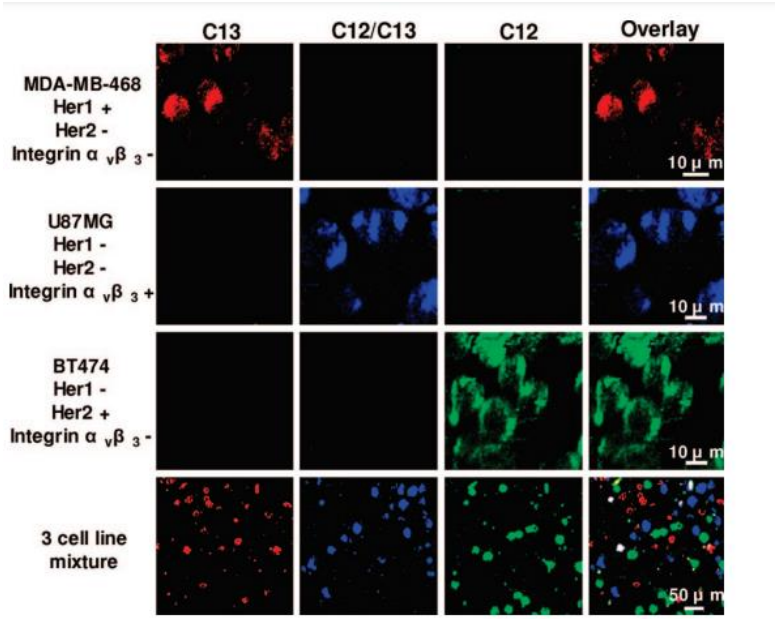

Figure 5: Multicolor Raman imaging with SWNTs. (Liu, Li, et al., 2008).

3.4 Magnetic Resonance Imaging

A whole-body image may be acquired with MRI without a depth restriction, making it a very potent tool. The use of contrast agents is employed in about 30% of the 60 million MRI operations that are performed annually on patients. There are two types of contrast agents for MRI: T1-shortening agents (which contain transition metal ions like Gd3+ and Mn2+) and T2-shortening agents (for example, iron oxide NPs). It is generally known that CNTs are capable of being doped with metallic impurities during the synthesis procedures, making them suitable for use as contrast agents in MRI without the need for extra processing. In reality, a lot of research has already been done to determine how effective CNTs might be for this. (Hwang et al., 2017). In one such investigation, Sitharaman et al. examined the relaxometry, phantom MRI, and magnetic behavior of gadolinium-catalyzed SWCNTs (Gd-SWCNTs). The T1-weighted MRI signal intensity of the Gd-SWCNT phantom solution was shown by the authors to be 14 times greater compared to the commercial Gd-based clinical MRI contrast agent (Magnevist). These findings imply that Gd-SWCNTs have the potential to function as extremely effective MRI-NIR imaging contrast agents. (Hwang et al., 2017). According to Richard et al., stearic acid was used in the manufacture of amphiphilic gadolinium (III) chelate (GdL). In this analysis, the scientists assessed the potential use of the aqueous GdL solutions embedded into MWCNTs (MWCNTs/GdL) as T1 and/or T2 contrast agents for MRI after stabilizing the solutions at concentrations ranging from 1 mM to 1 M. In order to do this, the functionalized nanotubes (MWCNTs/GdL) were injected intramuscularly into the mouse legs.

The outcomes adequately proved that MWCNTs/GdL could serve both as negative and positive paramagnetic contrast agents. (Richard et al., 2008).

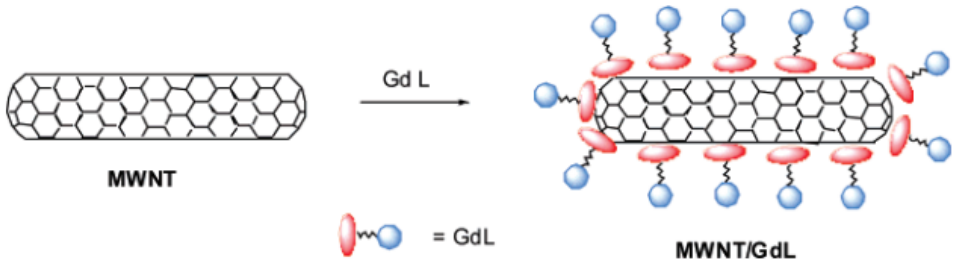

Figure 6: Carbon Nanotubes noncovalently functionalized by amphiphilic Gd3+ chelates. (Richard et al., 2008).

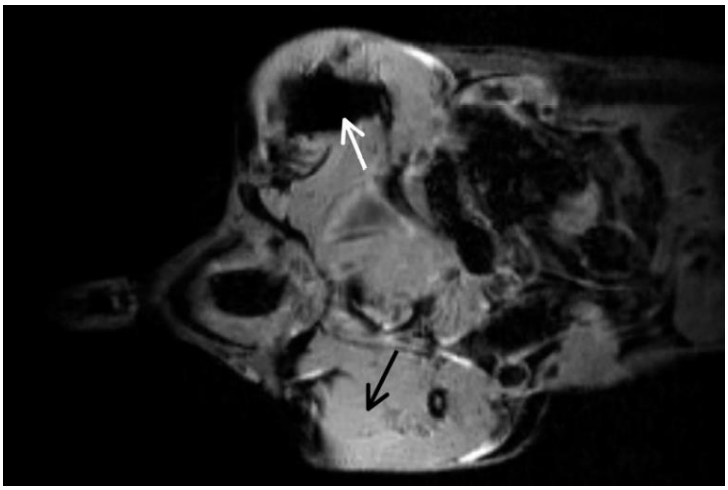

Figure 7: Coronal in vivo MR image of the muscle of the mouse legs after MWNT/L injection (left leg, white arrow) and lipid L injection (right leg, black arrow). (Richard et al., 2008).

In addition, Peci and coworkers created functionalized CNTs that might be employed as MRI contrast agents and as a substance for magnetic hyperthermia-based targeted cancer therapy. A central capillary was filled with iron NPs in their investigation to introduce CNTs with ferromagnetic characteristics, as well as the sidewalls of such CNTs were functionalized with Gd3+ ions. The Gd-doped CNTs of the enclosed iron NPs met the clinical criteria for hyperthermia treatment because their ferromagnetic characteristics at room temperature were preserved following surface functionalization. These hybrid structures have a large number of possibilities as options for MRI and magnetic hyperthermia cancer therapy, according to their findings. (Peci et al., 2015).

3.5 Biosensing/Immunoassay

The development of novel technologies for accurate early cancer detection from bodily fluids with an adequate spatial resolution for early diagnosis, based on the molecular fingerprints of proteins abundantly expressed in tumor cells, using minimally invasive procedures continues to be of great priority. The best option is to use antibody-conjugated CNT field effect transistor-based bio-conjugated label-free nanotube-based electronic equipment biosensors, which have the advantages of being inexpensive, requiring little sample volume, offering a direct electrical readout, and having the capability to carry out multiplexed identification from any biomarkers, the majority of which primarily depend on antigen-antibody reactions. Figure 8 displays the nanotube-based sensor's device construction. The device demonstrated p-type transistor activity with biomolecules adsorbed on CNTs by connecting the source and drain electrodes with a conducting channel constructed of nanotubes.

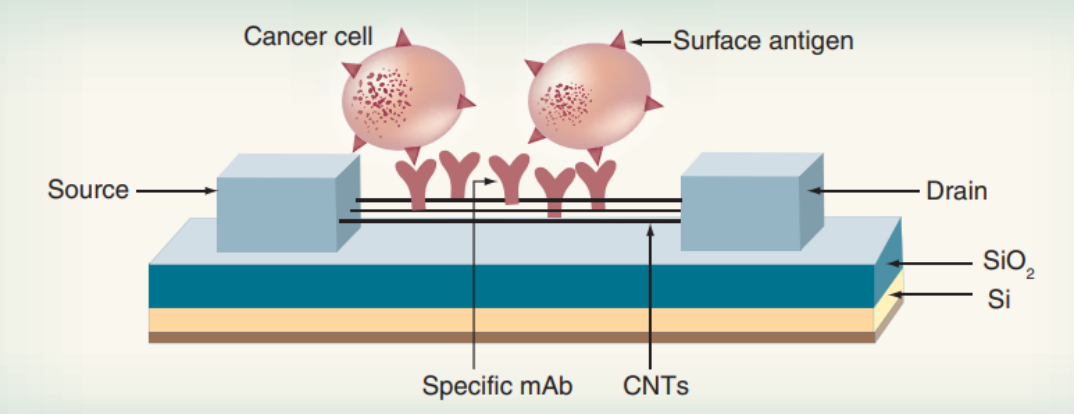

Figure 8: A diagnostic electrical device based on transistors made of carbon nanotubes. (Thakare et al., 2010).

Chapter 4

Application of Carbon Nanotubes (CNTs) in Cancer Treatment

Surgery continues to play a significant role in early-stage cancer survival by eliminating detectable tumor among all cancer treatment choices, including chemotherapy, radiation, immunotherapy, and thermotherapy etc. Chemotherapy and radiation therapy are necessary for cancer patients who have advanced disease and have undergone curative surgical operations. Even for patients who have undergone radical excision of a tumor, radio chemotherapy and other therapies are occasionally advised to stop relapse brought on by untreated micrometastases. Due to the lack of selectivity in these treatments, systemic toxicity may arise even though these methods are sometimes effective. With the right surface changes, carbon nanotubes carrying abilities, and special physicochemical characteristics can create a new class of nanomaterials for treating cancer. (Ji et al., 2010).

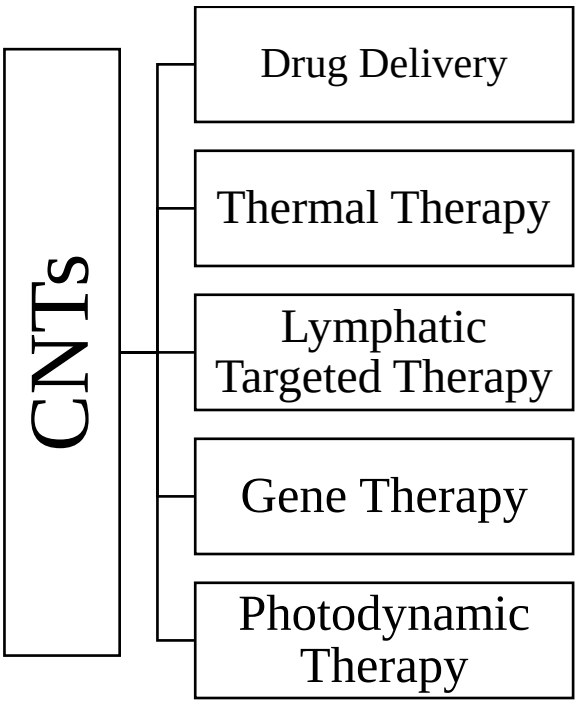

Figure 9: Carbon nanotubes with multiple uses for treating cancer. (Ji et al., 2010).

4.1 Drug Delivery by CNTs

Since chemotherapeutic drugs lack selectivity, their traditional administration is frequently impaired by systemic toxicity. The clinical administration of chemotherapeutic medications is further constrained by factors like inadequate distribution across cells, low solubility, the difficulty of pharmaceuticals to penetrate cellular barriers, and, most importantly, a lack of

clinical techniques for treating cancer that is multidrug-resistant (MDR). These issues have been the focus of extensive research globally in recent years. In addition to emulsions, quantum dots, polymers, silica nanoparticles, micelles, dendrimers, liposomes and molecular conjugates, a large variety of other forms of drug delivery methods have also been studied. Moreover, many other useful compounds, including medicines, peptides, and nucleic acids, can be incorporated into the walls and tips of CNTs according to their exceptional features, particularly their ultrahigh surface area. (Ji et al., 2010). Researchers have discovered that functionalized CNTs may pass through the membrane of a mammalian cell using endocytosis or other processes. (Bhirde et al., 2009). CNTs are excellent candidates for drug delivery because they may transport therapeutic medications more securely and effectively into cells that were previously out of reach with the aid of particular peptides or ligands on their surface to detect cancer-specific cell surface receptors. (J. Chen et al., 2008). Figure 10 shows a SWCNT-based drug delivery system that can administer medications for the treatment of cancer.

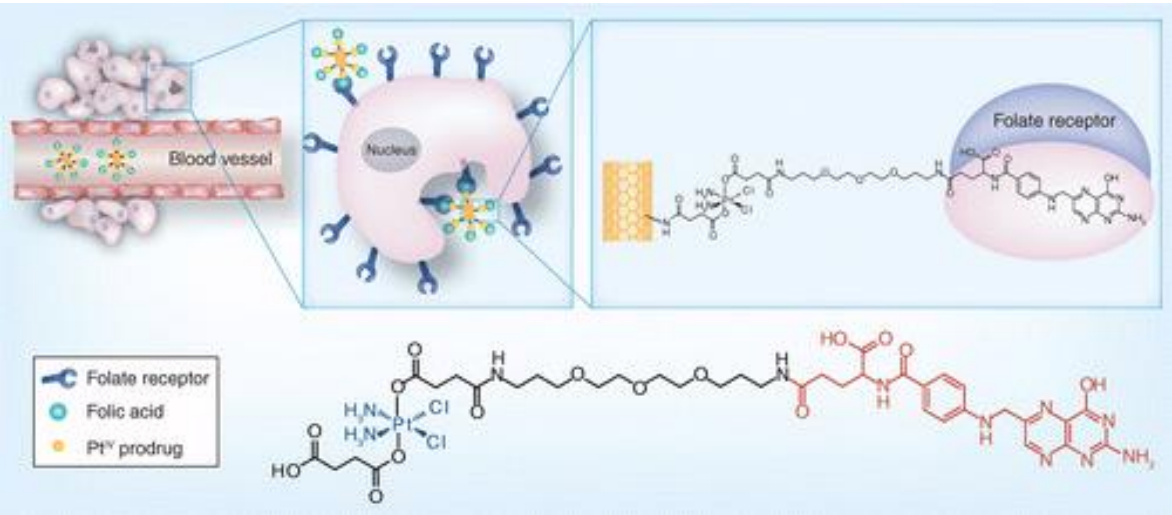

Figure 10: Single-walled carbon nanotubes coupled with a platinum-containing cancer treatment and its subsequent endocytosis for folate-mediated cancer targeting. (Thakare et al., 2010).

Currently, some researchers have already created innovative SWNT-based tumor-targeted drug delivery systems (DDS) (Table- 4). Functionalized SWNTs, tumor-targeting ligands, and anticancer medicines are the three main components of these delivery systems. DDS may be able to identify cancer-specific receptors located on the cell surface and then trigger receptor-mediated endocytosis when they come into contact with cancer cells. As a result of the complex's efficient and targeted uptake by cancer cells, chemotherapeutic drugs were released intracellularly, suppressing the growth of cancer cells more effectively than they did in untargeted controls with the same medication. (Ji et al., 2010).

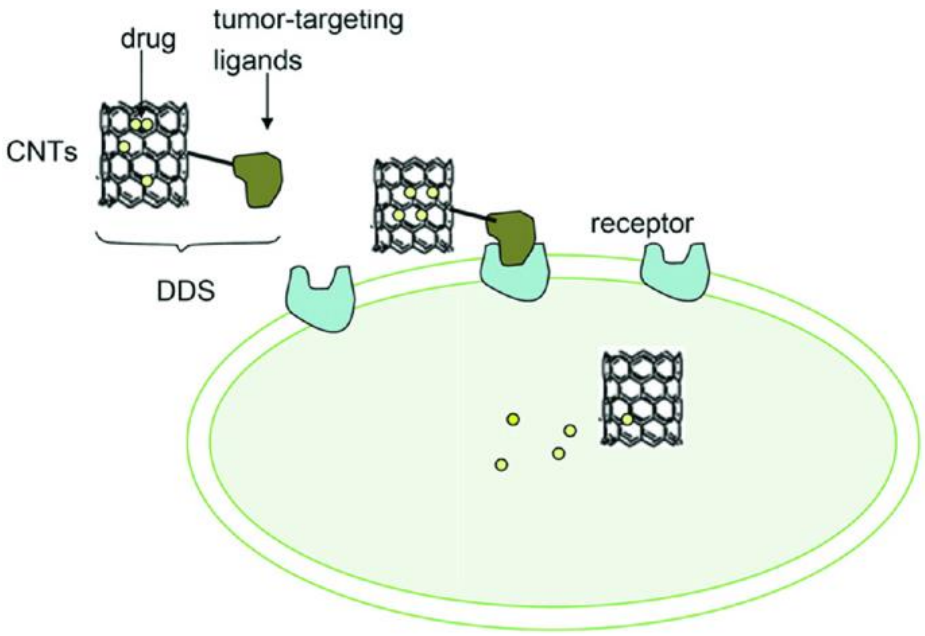

Figure 11: CNTs, ligands for drugs, and tumor targeting in a CNT-based tumor-targeted drug delivery system (DDS). (Ji et al., 2010).

Table 4: CNT-based tumor-targeted drug delivery systems (DDS). (Ji et al., 2010)

CNTs	Drug	Tumor-Targeted Modules	Tumor
SWNTs	Taxoid	Biotin and spaces	Leukemia
SWNTs	Doxorubicin	A monoclonal antibody	Colon cancer
SWNTs	Cisplatin	Epidermal growth factor	Squamous carcinoma
SWNTs	Cisplatin	Folate	Nasopharyngeal epidermoid carcinoma
SWNTs	Doxorubicin	Rgd	Breast cancer
SWNTs	Paclitaxel	-	Breast cancer

Nevertheless, the cytotoxicity was somewhat reduced with this unique technique, potentially preventing serious and harmful side effects. In a mouse 4T1 breast cancer model, SWNT-paclitaxel (PTX) conjugates also showed more efficiency in reducing tumor development than clinical Taxol alone, likely as a result of enhanced permeability and retention (EPR) in the tumor and prolonged blood circulation time. (Liu, Chen, et al., 2008). In addition, SWNTs

have a larger capacity for drug loading than those reported for traditional liposomes and dendrimer drug carriers due to their extremely high surface area per unit weight. Furthermore, the CNTs' inherent stability and structural flexibility may enhance the bioavailability of drug molecules coupled to them and prolong the period that the drug molecules are in circulation. Thus, these benefits demonstrated that CNTs can be utilized in future targeted delivery systems. (Z. Chen et al., 2017).

4.2 Thermal Therapy

CNTs are also accepted in the field of thermal therapy and are regarded as a non-invasive, safe, and very effective method due to their unique physicochemical features. CNTs have the ability to absorb light in the near-infrared (NIR) range, which heats the nanotubes. This special characteristic of CNTs has been used to produce heat effects that destroy cancer cells. (Elhissi et al., 2012). According to Biris, infrared photothermal (PT) radiometry was a very helpful instrument for assessing the temperature dynamics in scattered particular cancer cells or their clusters labelled with carbon nanotubes, which was beneficial in defining the optimal dose regimes for laser PT therapy utilizing relatively long laser pulses. The method, according to the researchers, may be especially beneficial for treating micrometastases, tumor margins, and small tumors. (Biris et al., 2009).

In a study by Gannon and associates, Kentera, a polymer made of polyphenylene ethynylene, was used to functionalize SWNTs. The formation of apoptotic cells that resulted in the total necrosis of the tumor cells served as evidence that the incubation of the nanotubes with hepatic cancer cells followed by the application of a radiofrequency field induced a concentration-dependent thermal death of the tumor cells. On the other hand, tumor cells that were injected with Kentera alone (without CNTs) remained alive after the radiofrequency field was applied. (Gannon et al., 2007). Folate-containing nanotubes with a diameter of 0.81 nm and a maximal absorbance of 980 nm have been utilized to treat cancer using photothermal therapy. When the tumor cells were subjected to 980 nm laser radiation, the cancer cells were photothermally destroyed both in vitro and in vivo studies. (Elhissi et al., 2012).

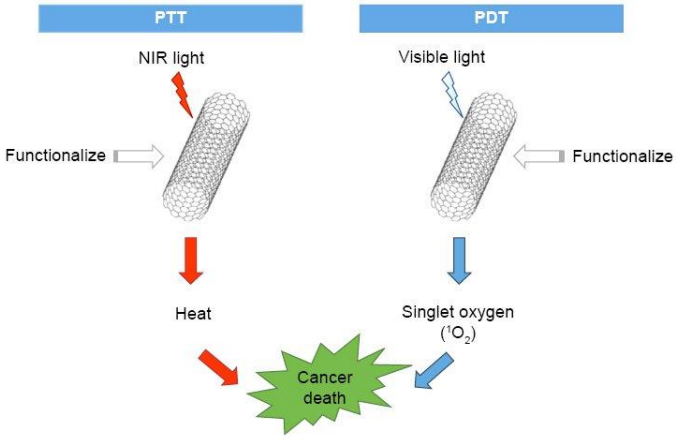

Figure 12: CNT-based methods for photodynamic therapy and photothermal therapy. (Son et al., 2016).

4.3 Lymphatic Targeted Therapy

Additionally, even after substantial lymph node dissection, malignancies frequently experience lymphatic metastasis, which causes frequent tumor growth. In order to solve this problem, magnetic multi-walled carbon nanotubes (mMWCNTs) were used to create a lymphatic focused medication delivery system that successfully and efficiently delivered gemcitabine to lymph nodes. No observable signs of systemic toxicity were seen. The conclusion points to a potential benefit over the way chemotherapeutic medicines are currently administered to lymph nodes by this unique drug delivery mechanism. In a different method, in situ polymerization of acrylic acid in a weak solvent for poly acrylic acid (PAA) was used to create water-soluble multi-walled carbon nanotubes (MWCNTs). Following subcutaneous injection of PAA-grafted MWCNTs (PAA-g-MWCNTs) into a rat's left back foot pad, a biopsy revealed that the left popliteal lymph nodes were darker than the surrounding areas 24 hours later. Rats injected with PAA-g-MWCNTs also had substantial accumulation of black particles, according to micropathology, in their popliteal lymph nodes. However, the significant internal organs like the liver, kidney, and lung did not show any signs of PAA-g-MWCNT presence in the biopsy trials. It suggests that even when lymph nodes are very small, PAA-g-MWCNTs may have the potential to be employed as a vital coloring dye and make it easier to identify lymph nodes during surgery. (Ji et al., 2010).

In a related study, M. Pramanik and his associates used carbon nanotubes' inherent optical absorbance to create contrast agents for photoacoustic tomography (PA). In an in vivo rat model, they were employed to carry out non-invasive imaging of the sentinel lymph node (SLN). Over the NIR wavelength window, it was discovered that the PA signal from SWNTs in the SLN was greater than that in the blood (740–820 nm). They think that in the future, the

novel technique may serve as an effective pre-clinical and maybe a non-invasive clinical tool to detect SLNs of breast cancer. (Pramanik, Song, et al., 2009). The outcomes discussed above show that carbon nanotubes can be successfully targeted to lymph nodes, which may offer tremendous promise for the treatment or the prevention of tumor metastasis and may have a significant impact on the prognosis of cancerous tumors.

4.4 Gene Therapy

As previously mentioned, one of the primary uses of CNTs in the treatment of cancer is drug delivery. Additionally, it was shown that CNTS might be used for gene delivery, which would then lead to gene therapy and possibly the treatment of cancer. The development of vectors with the ability to effectively introduce genetic material into target cells while providing the least amount of toxicity is essential for the success of gene therapy. Because of their effective transfection efficiency, viral vectors remain the subject of the most research among the many gene carriers. Non-viral delivery systems are an appealing alternative, nevertheless, due to several limits and safety worries around the use of viruses in humans. The ease of usage, large-scale manufacture, and lack of a specific immune response makes non-viral vectors particularly suitable. Recently, a number of innovative non-viral vectors have already been developed that are similar to viruses in terms of transfection effectiveness. CNTs stood out among them due to their simplicity in penetrating the cell membranes and reduced immunogenicity. (Sanginario et al., 2017). Due to their ability to enter cells through an endocytosis process and their functionalization, CNTs appear to be an excellent nonviral vector for gene therapy since they allow the transfer of DNA without any degradation. One of the relevant studies looked into the transport of siRNA to tumor cells utilizing liposomes and functionalized MWCNTs. The results demonstrated that the siRNA provided by MWCNTs effectively inhibited tumor growth. (Madani et al., 2011). For example, Guo states that the inhibition of polo-like kinase 1 (PLK1) by functionalized MWCNTs with the appropriate siRNA will prevent the growth of cancer cells (lung cancer in this case). Through intratumoral injections, they contrasted CNTs with cationic liposomes as vectors. In contrast to cationic liposome complexes, which are typically administered systemically, they discovered that siPLK1 with MWCNTs increased its uptake by cancer cells in solid tumor mass in vivo. This resulted in a significant PLK1 knockdown. (Guo et al., 2015). To suppress the genes of a melanoma model, Siu's group non-covalently functionalized CNTs with a polymer (succinated polyethylenimine) and a siRNA fragment. They discovered considerable siRNA absorption and a functional gene-silencing action in the

tumor tissue. Over a 25-day period, this therapy reduced the growth of the tumor. (Sanginario et al., 2017). These examples demonstrate the enormous potential of both gene therapy alone and in combination with carbon nanotubes in the fight against tumors. As a result, we think that gene transfer vectors based on carbon nanotubes will be very important in the future for the treatment of cancer.

4.5 Photodynamic Therapy

Another area of research that is now being looked into is the use of CNTs as a brand-new photosensitizer for photodynamic therapy (PDT). It is widely known that the most widely used cancer therapies, such as surgery, radiation therapy, and chemotherapy, all have a propensity to suppress the immune system. PDT, on the other hand, has the potential to be the perfect cancer treatment since it is a focused therapy that may effectively remove tumors while also preparing the immunity of the body to find and eliminate metastases. (Ji et al., 2010). One of the most significant substances produced during PDT is singlet oxygen ($^1O_2$), which can quickly interact with cellular components and mediate cytotoxic effects to cause cell damage and ultimately cell death. The lifespan and diffusion range of singlet oxygen are highly limited. In order to ensure more effective, dependable, and selective PDT, Zhu developed a unique molecular complex consisting of a photosensitizer (an ssDNA aptamer, and single-walled carbon nanotubes) for these purposes. This combination was able to manage and regulate singlet oxygen formation. There is currently little understood about photodynamic treatment based on CNTs, thus more study is required. (Zhu et al., 2008).

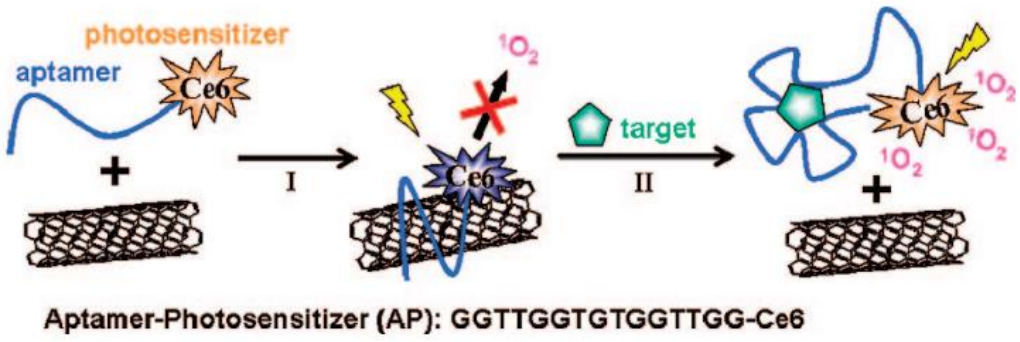

Figure 13: Diagram showing the control of singlet oxygen generation (SOG) upon target binding by the aptamer-photosensitizer-SWNT complex. (Zhu et al., 2008).

Chapter 5

Limitations and Future Perspectives

There are a number of restrictions on the therapeutic uses of these techniques, despite the fact that numerous research has demonstrated promising outcomes for CNT-based therapeutics in vitro and in vivo. Firstly, there has not been enough attention paid to safety concerns in the human body. The majority of in vivo toxicity testing were performed within a brief period of time, even though several in vitro tests demonstrated the safety of f-CNTs. The topic of long-term safety is receiving more attention, and in vivo research on the long-term toxicity and exogenous excretion of CNTs has made some progress. Additionally, CNTs have been purified and functionalized on the surface in an effort to reduce toxicity. Secondly, it is necessary to enhance the size uniformity of manufactured CNTs and the uniformity of the loading amount at drug-CNT complexes. Over the past few decades, a variety of tactics, such as controlling the growth temperature, the synthetic catalyst, ambient gas pressure, flux, and feedstock gas composition, have been suggested and investigated in an effort to improve the uniformity of CNTs. Different functionalization techniques involving covalent or non-covalent surface binding of molecules have now been implanted to CNT-based drug loading devices to improve loading uniformity. Additionally, it is necessary to enhance the controllability of loaded medications and the precision of targeting cancer cells. The functionality and stability of drug-CNTs have been reported to be improved by a variety of CNT functionalization techniques using a variety of compounds and materials, as was previously mentioned. (Son et al., 2016). CNTs will become one of the most significant tools in a variety of different biological sectors as well as cancer therapy with further research improving these techniques for practical application.

Chapter 6

Conclusion

CNTs have drawn a lot of interest in the biomedical areas due to their distinctive structures and characteristics, including as high aspect ratios, sizable surface areas, a wealth of surface chemical capabilities, and size stability on the nanoscale. The use of CNTs in the fight against tumors has resulted in a number of promising results in recent years, but much more research is still required before they can be used in the clinic. The main issue and practical limitation that needs to be addressed is the potential long-term toxicity. Although many efforts have been made to address this problem, particularly with a polymer coating and induced biodegradation, more work is still required to produce a very stable and non-toxic hybrid. With these presumptions, they have a strong chance of becoming the tumor nano-theranostic tool of the future, which combines diagnostic and therapeutic qualities in a single nanometric agent and may bring new options for the treatment and diagnosis of cancer. CNTs are excellent carriers for the delivery of chemicals, medicines, and biomolecules. When CNTs are properly functionalized, they can be used as nano-carriers for anticancer treatments. Due to their ability to take advantage of a variety of imaging techniques, including photoacoustic (PA) imaging because of increased ultrasonic emission as a result of significant NIR absorbance, fluorescence imaging because of enhanced fluorescence within near-infrared (NIR)-II biological transparent window, and magnetic resonant imaging, CNTs are the most widely used materials to visualize targeted tumors in cancer imaging studies.

In conclusion, because of their remarkable features, carbon nanotubes have enormous potential for molecular diagnostics and targeted treatment of malignancies. These therapeutic agents include imaging agents, targeting ligands, chemotherapeutic medicines, SiRNA, and many others. Before they may be advised for common clinical use, a thorough comprehension of both the pharmacological and toxicological features of carbon nanotubes as well as a fair assessment of the risk/benefit ratio are necessary.

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