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CARBON NANOTUBES AS AN EFFECTIVE METHOD FOR ANTI-CANCER DRUG DELIVERY: A REVIEW

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ABSTRACT: Cancer is a diverse category of diseases involving the growth of unchecked cells. Cancer cells uncontrollably divide and expand, creating malignant tumours that can invade surrounded parts of the body. Carbon nanotubes (CNTs) consist solely of a carbon atom organized into a tubular form in a sequence of condensed benzene rings. These sheets are rolled at a particular and distinct angle and the properties of the nanotubes are determined from the combination of the radius and rolling angle. Because of their non-toxic nature and high fluorescence characteristics, carbon nanoparticles are shaped into a ligand that is unique to a highly expressed receptor for imaging and drug conveyance in malignant growth care. Carbon specks (C-dabs) and carbon nanotubes (CNTs) are leading the continuous discovery of carbon-based nanoparticles. CNTs are used as nano-carriers for anticancer drugs, including carboplatin, camptothecin doxorubicin *via* proper functionalization.

INTRODUCTION: There are more than 1.16 million newly diagnosed cancer cases are being reported annually in India. Thus, in India, more than one out of three people are destined to develop some type of cancer during their lifetime [1]. Breast cancers, lung cancers, and oral cancers are the most commonly found cancer types amongst all the other types that are diagnosed in the Indian population. Thus, the most common causes of cancer-related deaths are due to lung cancer and breast cancer. Currently, radiotherapy, chemotherapy, surgical resection, or an amalgamation of these three modalities is used.

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The existing cancer therapy [2]. Despite the advances that are being made to improve the treatment efficacy over the last few decades, formulations (tablets, pills, injections) of many anti-cancer drugs still pose several problems, such as destructive "bystander" and the impact of the systemic toxicity on the surrounding normal cells.

Furthermore, some chances of vascular toxicity, nephrotoxicity, neurotoxicity, thromboembolic complications, Infertility will be there. Other side effects also include nausea, hair loss, and myocardial infarction, *etc*. are which can be expected. Other issues with traditional chemotherapy include the failure of the drug's ability to directly reach the tumour sites [3]. For these obvious reasons, the two key fields discussed by various groups of scientists are the demolition of malignant cells with minimal effect on other body cells and the administration of required doses of drug molecules to the sites of cancer for optimal

therapeutic effectiveness [4, 5]. In the last few years, due to development in synthetic chemistry, various biological nanomaterials that can be used have been created for various biological therapies, like the diagnosis of cancer, drug delivery, *etc.* [6]. This nanomaterial category contains quantum Dots, Dendrimers, nanotubes of Carbon (CNTs), silver and gold liposomes, Micelles, and nanoparticles 7, [8, 9]. One of the most popular nanomaterial for the various application in biomedicine, CNTs have drawn considerable attention owing to their unique properties [10]. CNTs tend to be more dynamic in their biological application as compared to other nanomaterial. For instance, cancer cell imaging alone is the main application of quantum dots, while CNTs are not only useful in imaging but can also be used for thermal ablation and in the delivery of drugs [2].

The main key areas of concern for various research groups have been the use of CNTs for drug delivery at the cation sites. This is due to the primary characteristics of these materials, which include their particular biological, chemical, and physical characteristics in the form of nanoneedles; the hollow monolithic structure, and their property to get obtained the desired functional groups on their outer layer [10]. Furthermore, the structure of the CNT can enable them to penetrate the cell through various mechanisms, like endocytosis or passive diffusion through the lipid bilayer, through which the CNT attaches to the cell surface and is eventually attached by the cell membrane [10, 11].

The hollow monolithic arrangement of CNTs and their potentiality to bind with desired functional groups makes them a favourable drug carrier of various anti-cancer and chemotherapeutic agents. In order to be more serum-stable and water-soluble, they can be functionalized with less toxic effect at the cellular level [10, 12]. CNTs mechanism of cellular absorption in the reports has been of great interest techniques have been explored to explain and numerous this notion. The marking of CNTs with fluorescent materials, like quantum dots, makes it possible for the scientist to trace the movement of the CNTs [13]. Besides, non-labelling techniques like atomic force microscopy or transmission electron microscopy have also been performed to detect CNTs [10, 14]. The process by which biological molecules are attached to CNTs can vary *via* a functional group. Biological molecules and drugs may either be loaded inside or bind on the surface of the CNTs. These approaches are also known as filling or wrapping modes of binding [16]. The consideration is to enhance their hydrophilicity. While functionalizing the CNTs, this can be accomplished by treating them with strong acid to modify the CNTs. As this acid treatment will result in the formation of a carboxylic group on their surface, enhancing their dispensability in aqueous solutions. Alternatively, hydrophilic materials can be attached to the surface of the CNTs covalently or noncovalently [15, 18]. The immunogenicity, biocompatibility, and hydrophilicity of CNTs can be enhanced by polyethylene glycol (PEG) coating [9, 19].

Basic structure and method of preparation of CNTs: In the 1990s, during fullerene synthesis as a by-product, Iijima and colleagues discovered carbon nanotubes. Carbon nanotubes are formed from graphene, wrapped sheets with two end caps just like semi-C 60 [20]. Carbon nanotubes are classified primarily into two different types, *i.e.*, multi-walled CNTs (MWCNTs) and single-walled CNTs (SWCNTs). SWCNTs are single graphene cylinders, offer imaging support, smaller in diameter, and flexible. While MWCNTs are complex nesting of graphene cylinders, having a more efficient endohedral filling and a high surface area [21, 22, 23]. The low-temperature Chemical Vapour Deposition (CVD) technique is the most widely used technique where alignment, length, purity, and diameter of CNTs are altered by differing several parameters, *i.e.*, catalytic particle size and roughness, type of metal catalyst, different precursor gas, the flow rate of gas, the temperature of CVD and run time of CVD.

The growth of the CNTs is done in the CVD chamber, which employs a gaseous form of carbon precursor fluxed with a carrier gas inside a reactor chamber, and to kick starts the chemical reaction, the presence of a metal catalyst is required [24]. Two main mechanisms that are accountable for the catalytic growth of the CNTs got their name from the catalyst concerning the substrate: base-growth and tip-growth [25]. In the base-growth method, the catalyst stays in its pristine position, although the entire nanotube flees away from the nearby catalyst [26]. In the tip-growth method, during the growth of

SWCNTs, an active catalyst moves forward and is separated from the substrate [27]. In these processes, beneath the reaction conditions, the carbon precursor decomposes on the metal particles. The terminated carbon atoms thus create a honeycomb-like tubular structure, which rapidly diffuses through and over the metal particles because of their extreme mobility on the metal surface. Other than this laser ablation, the arc-discharge method can also be utilized to procure the CNTs. In the arc-discharge method, an AC or a DC arc discharges between the two electrodes of carbon (amongst them, one is pure) in the presence of an inert gas that filled the chamber [28]. Laser ablation technique, which is almost similar in function to the arc-discharge method, but differs only in the use of a laser as the energy hitting the graphite containing a catalyst. In this case, CNTs' properties are influenced by several factors such as laser operating mode, target material, wavelength, pressure, laser peak power and laser energy [29, 30].

Due to the appearance of these metal catalysts (*i.e.*, nickel and iron), all of these methods of production of CNTs require a supplemental purification process before their use. Thus, CNTs are purified by oxidizing them with strong acids. This is also the most extensively used technique for the post-production purification of CNTs. However, this technique gives rise to the carboxylic acid functionalized CNTs but also can cause the breaking of the CNT tubes. Instead, it is better to perform the purification of the CNTs by using either a chromatography technique or by filtration or by centrifugation, as shown in several studies [31, 32, 33, 34].

Functionalization: Due to the highly hydrophobic nature of raw carbon nanotubes, they are insoluble in water solution, although pristine CNTs are insoluble in any solution. Functionalization can very much be an answer for this problem. CNT functionalization is a process of chemical synthesis technique. It is possible to add desired functional groups on the walls of CNTs that generate functionalized carbon nanotubes (f-CNT) for different uses. In cancer treatment, the purpose of this method is to enhance biocompatibility within the body, boost encapsulation propensity, solubility, delivery of multimodal drugs. It is possible to break modifications to CNTs into following two categories; covalently and non-covalently bonded.

Covalent Bonding: The potent chemical bonds between the attached molecule and nanotubes result in the covalent bonding of polymer chains to CNTs. In grafting molecules, various covalent reactions have been established based on their different properties. It is possible to further characterize these properties as Grafting to or Grafting from reactions involving the polymerization of monomers from surface-derived initiators the addition of preformed polymer chains on CNTs. There are three key methods used to covalently bind polymer chains or molecules that react with the superficial layer of pristine, pre-functionalist or oxidized CNTs. CNT oxidation is one of the most common modifications that use oxidizing agents such as concentrated nitric acid to form carboxyl groups at the most reactive sites, *i.e.*, the ends that are more reactive and any wall defects, such as 5-membered rings [35, 36, 37].

Compared to flat graphene the curving in the CNT puts a strain on the sp2 hybridized carbon atoms decreasing the energy bar needed to transform the sp2 hybridized bonds to sp [3]. This results in the sensitivity of pristine CNT to various additional responses such as the bingel reaction [35, 36, 37]. A strong attachment that is usually stable in a bio environment is given by covalent bonding. However, because of the damage to the CNT structure incorporates with covalent bonding, intrinsic physical properties of CNTs like Raman scattering and photoluminescence are significantly reduced. Because the use of these CNTs for imaging purposes or photothermal ablation cannot be functionalized using covalent bonding. To change carbon nanotubes to accommodate different applications, a variety of covalent functionalization reactions have been used [38].

Non-covalent Bonding: In CNTs the non-covalent bonding between the molecules is the most commonly used drug delivery process. There should be some unique properties of an ideal non-covalently functionalized CNT; the more similar they are matched, the more the utility is going to be there in their biological roles. It can be achieved by developing micelle-type structures in which the CNT is coated with amphiphilic molecules. This π-

π bonding attained by assembling pyrene molecules onto the CNT surface is another common type of functionalization. Because of the aromatic DNA base units, this bonding form can be extended to the single strands of DNA. As it is cleaved by nucleases, this was shown to be unstable, and biological uses are therefore so far minimal. Non-covalent bonding doesn't disturb the π-structure where the physical properties of the CNTs are basically maintained, except for a shortening of duration, indicating great promise for imaging and photothermal ablation [39].

The Applications of Cnts in Cancer Diagnostics: Radical resection is a successful way cancer in the initial stages of cancer, so treating initial diagnosis has become very significant for cancer treatment. Although, conventional imaging methods (e.g., CT, X-ray, and MRI) used in the treatment of cancer cannot provide adequate resolution in the initial diagnosis. In most early neoplastic disorders, there are no apparent morphological changes, so the patient can typically not be identified by these conventional imaging methods. It has become more important to find a dependable procedure to detect initial biological molecular interchanges before any morphological substitution. Positron emission tomography is highly sensitive and precise, as are evolutionary imaging techniques in the initial detection of cancer, and is focused on metabolic and biochemical changes. Some general radiopharmaceuticals used in the Positron emission tomography (PET) imaging modality is fluorodeoxyglucose (FDG).

It is not highly specific to cancer, but it is currently used by around 95% of medical imaging technology because it promotes metabolism [40, 41, 42, 43]. Therefore, finding new approaches for detecting and diagnosing early cancer is urgent. Certain classic proteins are normally over-expressed in cancer cells, which may provide an opportunity for early cancer detection. Several important tumour markers such as antigen 125 (CA125), Alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and prostate-specific antigen (PSA) have been commonly used in the diagnosis of certain cancers [44, 45]. However, these are only used in the subsequent ways; they involve assessing prognoses and forecasting clinical reactions, and maintaining supervision in operational therapy due to their poor sensitivity and early detection of cancer.

On the other hand, CNTs were proposed as an optimistic instrument to detect the expression of traditional biological molecules at an initial stage of cancer because of their specific electronic, thermal, and mechanical properties. New CNT-based methods with great sensitivity and ultra-low and wide liner detection were achieved. Besides, compared to traditional ELISA commercial test kits, the new CNT system will save time and achieve the same selectivity [46]. More significantly, portable equipment can be less costly than current methods, including immunoassays, test strips, and kits [47].

In the last few years, the discovery of biomarkers for cancer detection has become an emerging practice. Since radical tumour resection is the only early treatment option, initial screening and diagnosis have become critical in cancer treatment. Many cancers have no apparent signs at the beginning, and conventional cancer imaging methods don't have adequate imaging for early detection and prognostic evaluation. Some tissue changes serve as fundamental for the early detection of cancer, including mechanical characteristics, optical absorption, and RF absorption. New techniques for early cancer detection are very important. Here we give a new perspective on how nanotubes in the various diagnostic concepts were used.

Ultrasonography: The province of diagnostic imaging is important evolving and potential use of CNTs [48]. Ultrasonography is the common imaging method because of the intrinsic protection and low-test price [49]. Ultrasound is clinically implemented with sound waves varying from 2-12 MHz, with a structural resolution is 0.2-1mm. The exceptional properties of functionalized MWCNTs as ultrasound contrast agents showed by Delogu et al. [50]. They functionalized 1, 3-dipolar cycloaddition azomethine ylides (ox-MWCNT-NH_3) with MWCNT sand showed the functional MWCNTs had signal reactions equivalent to the contrasting commercial agent in comparison to other types of carbon nanotubes. Wu and his associates established a multi-label MWCNT approach that

focuses on tumour cells and utilizes properties of the MWCNTs as an ultrasound contrasting agent [51]. In his work, the polyethyleneimine (PEI) was used to co-functionalize MWCNTs accompanied by fluorescein conjugation PSCA monoclonal antibody (mAbPsCA) and isothiocyanate (FITC). These nanoprobes (CNT-PEI(FITC)-mAb) together have many roles, but the ultrasound contrasting agent and their ability to selectively target the desired tumour marker make them a suitable candidate of concern in this study.

Photo Acoustic Imaging: Photoacoustic (PA) imaging is also a common emergent and effective method close to ultrasound [52]. Like ultrasound, the signal output from PA images is an acoustic wave, except in the latter case, the light source is an induction to an acoustical source in the tissue area. The signal for the PA output is broadband. Certain tissues have a PA behaviour already, but many conditions do not display PA-contrast, so the use of an exogenous contrast agent is necessary [52, 53]. PA properties of pristine CNTs can easily be enhanced [54, 55, 56, 57, 58]. The challenge is targeting CNTs on the cancer scene to visualize them. This was solved by De la Zerda *et al. Via* the double CNT functionalization. The first one was to enhance the PA-performance by enhancing the optical absorbance by using π-π stacking interactions with Indo Cyanine Green (ICG). The second was cyclic Arg-gly-asp peptides on the surface of PEGylated CNTs targeted at αVβ3 integrins of the CNT that were overexpressed in tumour vasculature.

Kim *et al.* attempted an additional strategy to improve CNT PA response by using gold layered CNTs which is considered to have high absorbance in the near-infrared region (NIR). The final structure was also functionalized with a study that particularly recognizes mice's endothelium [59]. The Group of Wang unites two strategies to create RGD-coated silica-coated gold nanorods for a gastric tumour on the exterior of carbon nanotubes. The results indicate that nanoprobes accumulate in the regions with stomach cancer, and the PA signal has become stronger over time as a result of this accumulation [60].

Near-infrared imaging: The Near-Infrared (NIR) biological window shows strong intrinsic fluorescence and optical absorption (700-1400 nm) [61]. This property can be used *in-vivo* imaging with high resolution as non-photo bleaching fluorophores [62, 63, 64, 65, 66, 67, 68]. In addition, in the Near Infrared-I (NIR-I) window, the wavelengths of excitation decrease while the wavelengths of emission decrease in Near-Infrared -II (NIR-II, 950-1400 nm). Antaris and co-workers preferred one reactive CNT chirality only (6, 5) and injected very small quantities (4 μg) of CTNs in mice after a proper biocompatibility mixture. The results show that CNTs are injecting into the mouse and have high NIR emissions over time [69].

More recently, SWCNTs have been used by Ghosh *et al.* as a guideline for the operation of small tumours [70]. Besides, Ghosh and colleagues established M13 bacteriophage stabilized CNTs in order to mark the tuomur and show the characteristics of photoluminescence in a real case [66]. The outcomes indicate that after a sufficient period of diffusion very small parts of the tumour become apparent. Many of them with normal dye was not even visible. This approach will help to extract tumour masses even in the early stages by significantly improving their survival after treatment.

Magnetic resonance imaging (MRI)- MRIis one of the most effectual diagnostic instruments [71]. In order to match atomic magnetization of water inside the body, MRI does not utilize ionizing radiation, instead of a high-intensity magnetic field by utilizing the difference in concentration of water between tissues to create good quality anatomical images with great structural resolution [72]. There are two types of MRI contrast agents, spin relaxation agents with greater effects on T2 shortening and spin-lattice relaxation agents with greater effects on T1 shortening spin, in which the proton relaxation times are T1 and T2.

A super paramagneticco-paramagnetic urgent mst also be encapsulated to or conjugated within the CNTs to generate an MRI-active CNT CA, although some suitable agents are required to target tumours [73, 74, 75, 76, 77]. In recent years, Liu et al. have attached nanoparticles within MWCN Super Paramagnetic Iron Oxide (SPIO) inner spaces to generate a contrasting agent that is a T2-weighted agent. SPIO-MWCNT was coated with a polymer to inhibit aggregation and improve its vascular

biocompatibility [78]. The last polymer consists of 2 units of a very particular function: the cationic block of PMETAC was developed to bind the negatively-loaded, oxidized CNT electrostatically, and the second functional block of the PEGMA was developed to boost the aqueous stability of the hybrid material [79].

PET/SPECT: The Positron Emission Tomography (PET) is a non-invasively imaging tool that is used to monitor cellular activity employing a radiolabel molecular ligand (or tracer). PET is an essential tool in both research and clinical fields among nuclear imaging technology. Gamma rays releasing from a decomposed radionuclide inside the patient are identified by two rotating detectors and transform the observed energy into an electrical signal, which is later converted into an image. Radio nuclei release positrons in the pet imagery, which interact with the direct electrons, contributes to two extreme-energy photons. Two 511-keV photons are released at approximately 180 degrees in opposite directions from each other. The gamma rays are also found out along a given line of response by a ring of detectors that shows concurrent rays originate from a single case.

It is possible to conjugate or even inject positron-emitting radionuclides for PET imaging into CNTs. Liu et al. first shown to work radio labeled SWNTs for tumor-targeting PET imaging with arginine-glycine-aspartic acid (RGD) peptide-linked polyethylene-glycol (PEG) phospholipids. This complex resulted in an efficient, targeted, integrated tumour with a resulting good contrast picture [80]. Similarly, functionalization of other CNTs works on multimodality cancer theranostics which have been investigated for radio-labelled and tumour targeting biomolecules [81, 82, 83].

Two different types of MWCNT constructs were developed by Ruggiero and colleagues in which the E4G10 anticorder was introduced specifically for its in epitome expressed the tumourangiogenic vessels. Firstly, the efficient 225Ac3 + radionuclide generator was designed for alpha particulate emitting and secondly for the distribution of the 89Zr radionuclide for PET imaging. The second modification for PET imagery allowed them to increase specific behaviour approximately five times that improved the signal-to-noise ratio of picture [84]. Although achieving excellent cancer treatment outcomes with the first modification, it should be observed that a single CNT may be built to combine both therapeutic and imaging cargo into the first modification [85, 86].

Multimodality Imaging: At this point, it should be clear that any imaging technology has both advantages and disadvantages, preventing an approach from prevailing over another. The next optimal step is to incorporate all the benefits in a single strategy that eliminates all disadvantages. This is why several groups of research work on multimodal CAs that can maximize all the advantages of each method [87, 88, 89]. Due to the many types of capabilities that are possible in their application, CNTs are the perfect platform for this reason [90]. Cinsneros *et al.* built a CNT-based double CA. For MRI and PET, respectively, they have filled CNTs with Gd3 + and $64Cu_2$ +. Despite not having tested actual tumour, they have shown platform stability *in-vivo* over time and screened for mainly pulmonary and liver accumulation [91].

Similarly, a bimodal CNT CA for SPECT and MRI was developed and implemented by the Wang Group. Magnetic properties of Superparamagnetic Iron Oxides (SPION) were granted to CNT while a radioactive property was granted to 99mTc. No real tumours were identified even in this case, but stability, distribution, and aggregation of the organ were only investigated. Distribution studies indicate that the lung, liver, and spleen have accumulated prevalently, with an incremental reduction in lung absorption, while hepatic signals remain constant after 4 h. The images show the potential of the hybrids for in vivo use as dual MRIs and SPECT contrast agents [92].

Very recently, by integrating SWCNT, Zhao *et al.* developed a new CNT hybrid multimodal with Mn2 + for MR images and 131I for nuclear imagery and polydopamine (PDA) and PEG and radioisotope treatment for cancer. The author's observed efficient tumour accumulation of SWNT@PDA-131I-PEG following systemic mice administration, as revealed by MR and gamma scanning. Also, in combination with 131I-based radioisotope therapy, they utilize the heavy NIR absorption of SWNTs to conduct NIR-triggered photothermal therapy to achieve good results in

killing cancer [93]. These recently appeared multimodal contrast agents would be a precious instrument for tumour imaging, theranostic, and radiation guidance applications [94].

The Applications of Carbon Nanotubes in Cancer Therapeutics: In the initial stages, radical resection is the most successful means of treating cancer. Some methods have emerged with the advancement of biotechnology in recent years in the field of cancer care. However, a more effective method for precise chemo drug delivery still needs to be developed [95, 96]. In recent decades, different drug delivery mechanisms have been tested to administer certain chemicals to tumours, such as doxorubicin (DOX) and paclitaxel (PTX). Natural/synthetic polymers, Liposomes, and nanoparticles are used in these delivery systems. Sadly, inorganic compounds that have distinctive physicochemical properties are generally overlooked. CNTs have characterized features that make them ideal carriers for the delivery of drugs specifically targeted loadable. As drug carriers, CNTs have certain advantages, including rigid structure, thermal conductivity, are characteristics capable of post chemical changes, satisfactory surface-to-volume ratios, and outstanding biostability.

CNTs in Cancer Chemotherapy: The first step, which is the essential part of the effect of chemotherapy, is drugs for the treatment into various biological barriers. That involves renal and liver clearances, enzymolysis, endocytosis, hydrolysis, and lysosome degradation. There is poor stability, poor solubility, and high toxicity for some chemotherapeutic medicines in cells and tissues that have significant impacts on their efficacy. However, CNTs can boost the biodistribution and prolongation of the therapeutical blood circulation, increase pharmaceutical effectiveness, and decrease the use dose. Liu *et al.* designed a DOX loaded onto branched PEG-functionalized SWNTs in view of the fact that the biostable SWNT was built to extend the duration of blood circulation [97]. This SWNT-DOX complex has been injected into cancer mice. They found that it is possible to inject DOX into the tumour and that SWNT can be cleared by renal excretion from systemic blood circulation. However, because of their low aqueous solubility, physical loading of the PTX is very difficult.

Lay *et al.* had developed both PEG-graft single-walled CNTs (PEG-gSWNTs) and PEG-graft multi-walled CNTs (PEG-gMWNTs) to increase the loading capacity in order to overcome this hurdle. They found that in in-vitro, it is possible to maintain the transmission of PTX over 40 days [98]. With technological advancement, some researchers have changed the carrier of SWNTs to boost their delivery performance, such as delivering anticancer agent cisplatin mediated by the epidermal growth factor (EGF-) SWNT [99]. Besides, MWNTs can be used as a carbon-based nanomaterial for thermal ablation, resulting in hyperthermia that kills cancer cells.

Photo Thermal Therapy (PTT): Hyperthermia is a therapy that raises temperatures above the cellular level in the area affected by cancer in the body and thus contributes to cell death [100, 101, 102, 103]. If by optical radiation the temperature is increased, it is often referred to as Photo Thermal Therapy. The benefit of thermal ablation relative to operative tissue elimination is its minimum intrusive nature with decreased impermanence as well as the ability to cure tumours in a critical configuration that cannot easily be surgically removed. In conjunction with another medication such as chemotherapy or radiotherapy PTT can synergically improve cytotoxicity of the tumour [104, 105]. Hyperthermia also prefers to improve tumour vasculature permeability, thereby improving drug delivery to tumours [106]. The key factor in thermal ablation for cancer cells is to consistently exceed the threshold of cell heat resistance [107]. Many scientists' groups have created a new generation of hybrids for cancer phototherapy with high efficiency and performance as CNTs can turn almost infrared light into heat [108, 109, 110, 111, 112, 113].

The CNT's ability to transform NIR light into thermal energy brings on many scientists' groups to develop a new hybrid generation for high-efficiency cancer phototherapy. A new SWCNT compound with a peptide with a repeating structure of H-(-Lys-Phe-Lys-Ala-)7-OH ((KFKA)7) was formed by Hashida *et al.* (KFKA)7 has been equipped for wrapping SWCNTs and providing good water dispensability and stability. Both in-

vitro and in-vivo experiments have produced strong results, in reality, the hybrids directly injected into the 26-colontumour and the Near-infrared irradiation have instantly raised their temperature to 43 °C, causing the remarkable suppression of tumour [114].

The use of excellent NIR absorption by CNT is not the only way to raise its temperature [115, 116]. To prevent aggregation and injection into the tumour Gannon's group coated SWCNTs with a polymer. Subsequently, polymer-coated CNTs were exposed for two minutes to a 13, 56 MHz RF region. They found that the tumour has been totally eliminated in all test samples. In contrast, CNT-free tumours, but under the same RF area and CNT-free tumours remained viable. These results indicate that the treatment of CNT hyperthermia will cause non-invasive RF field therapy to develop lethal thermal damage to the cells [116].

Photodynamic Therapy (PDT): Aerobic metabolism continuously generates small quantities of Reactive Oxygen species (ROS) in organisms. In order to nullify certain toxic organisms called antioxidants living cells have some countermeasures. If the ROS is too high in concern with antioxidant, it led to a disorder referred as oxidative stress. If oxidative stress continues for a long period of time, it may cause cell death which is referred as apoptosis [117]. Cancer and Apoptosis are opposing conditions, but ROS is stated to play a significant part in both. ROS is purposely stimulated inside cancer cells to kill them during tumour treatment [118]. PDT is a technique that is minimally invasive using exceptional photo-sensitizers (PS), which produce ROS after illumination. Nanomaterials, particularly CNTs can play significant roles in this context [119, 120]. By functioning hyaluronic Acid (HA-CNT) CNTs, Shie et al. developed a new hybrid that makes them extremely solvable in water [121]. In the next step, a photodynamic agent known as Hematoporphyrin Mono-Methyl Ether (HMME) was adsorbed on top of HA-CNT.

In-vitro and *in-vivo* testing of their photodynamic and photothermal properties was performed on the samples. Comparison studies were performed for in-vivo tests. The tumor-bearing mice were divided into five classes and administered differently: 1) an HA-CNT and treated with a laser of 808 nm 2), a saline solution, 3) an HMME-HA-CNT and a laser of 532 nm;4) an HMME and a laser of 532 nm and 5) an HMME-HA-CNT which was treated with lasers of both 532 and 808 nm.

After eight days, they removed and analyzed the tumours. Control Groups 1, 2 and 3 do not have a major reduction in dimensions. On the other hand, in conjunction with NIR photothermal therapy (group 4), a group with PDT (Group 5) contributed to a significant reduction of the tumour and, even more significantly, to treatment [121]. Thus, there are good results for PDT in combination, especially with other treatments [122, 123, 124, 125, 126].

Drug Delivery System: The aim of chemotherapy is to destroy cancer cells and reduce side effects in healthy tissues. But several of today's chemotherapy agents are not suitable. Many of them are also extremely toxic. Also, it has other disadvantages, such as reduced solubility and low non-selective biodistribution. CNTs are used as targeted drug delivery in order to solve these problems [127, 128, 129, 130, 131, 132]. It is also described earlier, CNTs show properties that can be used to design magnificent nano-drug vectors. A bit of these feature, the increased EPR effect, needle-shaped forms that promote intracellular and transmembrane accumulation and easy loading of molecules in covalent and non-covalent interaction on the Surface or within the CNT's internal centre [133, 134, 135, 136, 137, 138, 139].

By wrapping it around the CNT surface, Ji *et al.* non-covalently functionalized SWCNTs with chitosan. The functionalization of chitosan made CNTs dispersible and more biocompatible in water. Ji's group further functionalized it with folic acid to target the new material only to the cancer cell since the folate receptor is over-expressed in many tumours. Finally, the well-known Doxorubicin (DOX) anti-cancer agent was attached. Therefore, in-vivo and *in-vitro* experiments were lead for the final hybrid to better kill tumour cells at dose levels much lower than DOX. The authors attribute to three major factors these good results: more effective targeting of the tumour because of folic acid, the good ability for CNTs to penetrate cells in terms of free DOX, and the fact that a DOX release occurs in a tumour-type low pH environment [140,

[141]. In addition, a lot of study goes to multifunctional CNTs so that they can act as contrasting agents in imaging during therapy [142, 143, 144, 145].

Gene Therapy: When we provide genetic information to the patient somatic cell which is required to produce proteins for the therapeutic action to modulate or cure disease is known as gene therapy [146]. Gene therapy is effective or successful when the developed vector is proficient in inducing genetic material with mild toxicity into the targeting cell. The most widely used gene carriers are viral vectors due to their effective transfection efficiency [147]. The non-viral delivery system is a good alternative because the use of viruses in humans is concerned with their safety and some other limitations [148].

Several on-viral novel vectors have been formed recently, which approaches viruses with reference to transfection ability [149]. CNTs have low immunogenicity and the ability to easily penetrate the cellular membrane, due to which they attract much interest [150, 151, 152, 153, 154]. For example, in a continuation of a previous study about delayed tumour growth, tumour apoptosis intake of small interfering RNA (siRNA)-functionalized MWCNTs complexes through intra-tumoral route was observed to have prolonged the survival of human lung xenograft-bearing mice [155], Guo *et al.*

Functionalized MWCNTs with a proper siRNA, whose effect is the restriction of polo-like kinase 1 (PLK1) that is predicted to hinder the reproduction of cancer cells (in case of lung caner). Cationic liposomes and CNTs compared to vectors employing intra-tumoral injections. It is found that siPLK1 with MWCNTs facilitated its internalization by cancer cells in solid cancer mass in vivo which resulted in remarkable PLK1 knockdown equate to cationic liposome complexes, although the latter complexes are usually injected systemically [156]. Silence genes of melanoma model are non-covalently functionalized by CNTs with a polymer (succinate polyethyleneimine) and to a siRNA fragment by Siu's group. They found a working gene silencing effect and significant uptake of delivering siRNA in the tumour tissue. Over a 25-day period, such treatment resulted in the attenuation of tumour growth [157].

Drug Targeting: Drug delivery is unavoidably indiscriminate in traditional cancer treatments using chemotherapeutic agents. This toxic drug treatment is accordingly administered to both regular and tumour cells, which have the effect of the toxicity of the drugs themselves leads to the death of the patient in the worst case, and the patient observes numerous unpleasant side-effects in the best case. If chemotherapeutic agents have been administered only to tumour cells, then this would allow more effective and reduce the inauspicious side effects; for traditional chemotherapy, concentrated doses will be toxic.

For conventional nanoscale drug delivery, there are mainly 2 methods, which include passive (or size mediated) targeting, which relies upon the growth behaviour of tumours and the unique size of the nanoparticles. It requires greater amounts of nutrients and oxygen for tumour growth, capture new blood vessels by a process known as angiogenesis. The endothelial cells, in a tumour can be 600 nm or more spaced from each other, unlike regular blood vessels. Nanoparticles' entry into the intestinal space is increased due to this defect. Also, in these tumorous areas, poor lymphatic drainage was there.

Together both of these effects are known as enhanced permeability and retention (EPR). To increase the density of the nanoparticle (and their therapeutic agent) locally in the tumour, we have to construct nanoparticle suitably, up to 10 times the drug concentration is increased by using nanoparticles [158]. To decrease the pH locally, a process known as glycolysis is used, which increases the energy level. Therefore, the nanotube is coated with a biodegradable substance that degrades at acidic pH within the cancerous tumour, for the controlled release dosage form [158].

Another method is active targeting which includes ligand-targeted binding or antibody-targeted binding used for selective drug delivery to the tumours or cancer cells. Several properties which are distinctive to tumour cells and having immense density to differentiate from surrounding cells, knowledge of antigen or target receptor is required for this technique [159]. In laboratory tests, research has shown that the latter method is used for nanoscale drug delivery devices, and cancer cells

are targeted specifically by this device. carbon nanotubes used as a potential delivery vehicle for therapeutic treatment and diagnosis instead of additional drug delivery vehicles and imaging agents such as robust silica-coated micelles for delivery of hydrophobic anticancer agents [160] spherical dendrimers or repeatedly branched by, (typically outer functional groups to the periphery of the molecules or covalent bonding [161]). Central to a nanoparticle's efficacy when it undertakes the body is its potential to detour the immune system for at least as long as it takes to reach and react to the cancer cells. For example, the mononuclear phagocytic system (MPS) clears the first-generation polymer-coated liposomes within min. Unlike the unmodified phospholipid liposome surface, the second generation has a modified liposome surface that does not attract the plasma proteins and MPS. Either actively or passively, liposomes circulating within the blood for much longer and are thus more likely to reach their target [162]. When nanotubes have used, similar techniques are required to ensure high circulation periods.

The temperature rise required to induce a form of hyperthermia in the cells, and this process of thermal ablation is a unique property attached with nanotubes to cause an increase of 100 °C, ultimately causing their death [163]. This is a universal way of demolishing any type of cancer. At present thermal ablation of tumour cells is done by radiofrequency-based heating of an ablation catheter which is placed into the tumour with the endorsement of an ultrasound transducer for imaging; when the catheter is in place, destroying the cells, radiofrequency energy is applied via the catheter into the tissue which is then absorbed as thermal energy.

This technique's success depends mainly on the surgeon's accuracy when the catheter is inserted. When exposed to near-infrared (NIR) light, more accurate, reliable thermal ablation is achievable without requiring an incision by using targeted nanotubes [164, 165]. NIR light's another phenomenon and potential use, in conjunction with CNTs is in the triggered release of the drug payload. It was established that six 10 second pulses at 1.4W/cm^{-2} intensity released a DNA cargo into the inhabited cell [166]. Enabling precise control of the therapeutic treatment, the release of the payload was not accompanied by cellular destruction. An additional advantage of the increased local temperature is the increased permeability of the tumour vasculature. This Resulting in more effective chemotherapeutic treatment due to improved drug uptake into the tumour. Improving the efficacy of treatment yet with reduced intensity, it is conceivable that CNTs could be utilized as both a means of thermal ablation and a drug-delivery vehicle [163].

Passive and Active Targeting: As the antibodies loose their specificity upon binding with drug molecules, previous attempts at antibody-mediated drug delivery have been largely unsuccessful. It was established that using nanotubes to support antibodies did not change their properties and so did not hamper their targeting abilities. Active or Passive targeting methods are a direct result of functionalization. Passive targeting is a consequence of inertness and physical size of the macromolecule, "hiding" it from the immune system. Through an innate immune system, but also functionalized with molecules/polymer chains such as PEG which do not promote an adaptive immune response, CNTs must be Nano sized to prevent cellular opsonisation (the susceptibility of the macromolecule to ingestion by phagocytes resulting in its destruction).

The CNT must also be of sufficient size, to utilize the EPR effects and so a trade-off is required. IN determining the degree of optimal functionalization as it is an easily controllable variable PEG is useful. Microspheres can lead to chemo embolism-type problems in the lymph nodes. This passive targeting can cause problems. Functionalization with nonmagnetic particles (*e.g.* iron oxide) and placing of a magnet at the desired location for extended periods allows for drug release over an extended period for such cases.

Active targeting needs functionalization with tumor-specific binding sites to selectively bind to tumour cells. Most of the cells of various cancers are well known to overexpress certain receptors. For Example, brain tumours showing typically 100 k to 900 k LDL (low-density lipoprotein) receptors. Functionalizing CNTs with LDL reduces uptake in other cells that have far fewer LDL receptors. This is also increasing uptake dramatically in the cancer cells.

Crossing the Blood-Brain Barrier: Brain tumours in unreachable by many drugs because of the presence of the blood-brain barrier. Destruction of brain tumours from drugs is prevented by the blood-brain barrier. CNTs alternate to other vehicles as they cross the blood-brain barrier; the problem is overcome by attaching a chemotherapeutic agent and CNTs [167].

Drug Delivery Targeted to the Lymphatic System: The lymphatic canal is the most promising place for the metastasizing of many cancers. Metastasis of cancer is blocked by the targeted delivery of the drugs to the lymphatic system. CNTs are substituted by polyacrylic acid (PAA), which makes them highly hydrophilic, using radical polymerization. On the surface of PAA-CNT magnetic nanoparticles based on FE_3O_4 are absorbed using the co-precipitation technique.

To make nanoparticle stable from clustering, they interact with the COOH groups of grafted PAA. Gemcitabine was loaded in CNT nanoparticle by stirring the solution containing gemcitabine, PAA-CNT, magnetic nanoparticles based on FE_3O_4 for 24 h, with 64% of loading efficiency. After that CNT is seen to absent in major organs such as the heart, kidney, lungs, spleen, and liver and seen only in the lymph nodes locally, after 3 hours of injection through a subcutaneous route. In the lymphatic system, gemcitabine cannot either distribute without the help of these nanoparticles-based delivery system [168].

Thermal Ablation of Cancer Cells: Thermal ablation may be a strategy utilized to eradicate injured tissues or cells by applying external magnetic force waves and raised the heat in the cancer growth treatment. Techniques like cryoablation, radiofrequency ablation and microwave frequency ablation square measure utilized in thermal ablation medical care. Also, this system is centred on ultrasound (US) and optical device light-weight [169, 170].

The extra edges of this system over the regular techniques square measure the versatility, economy and it additionally minimizesthe tendency ofcancer cells to unfold wide [171]. Notwithstanding, during this medical care, the choice of applicable heat delivery thanks to the cancerous cells may be a crucial and difficult subject [172]. Besides, existing heating techniques expertise problems and difficulties in separation between cancerous cells and healthy cells and tissues, prompting the hurt of close cells [173]. Consequently, the grouping of engineering and thermal ablation medical care has force in a very batch of consideration as a positive approach to beat the applicable restrictions of conventional heat therapies.

Kinetics: Carbon nanotubes as carriers for drug delivery, the administration, absorption and carrying CNTs ought to be taken under consideration to exploit the curative effects. Calculated routes of CNT dispensation contain oral and injections like, abdominal injection, subcutaneous injection and intravenous injection. Once carbon nanotubes square measure is administered by distinctive routes, their absorption and distribution additionally occur distinctively. Carbon nanotubes that square measure absorbed, carried by blood or bodily fluid circulation to the targeted sites. Absorption is at first the crucial stage for drug carriers to accomplish their mission of drug-delivery when administration.

It had been found that carbon nanotubes themselves square measure good of being absorbed. It has additionally been established that physically shortened CNTs that square measure administered orally may be absorbed by means that of the columnar cells of the intestinal mucosa, this was once tested with the help of the usage of transmission microscopy [174]. Once subcutaneously and abdominally administered, a phase of carbon nanotubes keeps inexhaustibly within the close tissues despite the fact a few of them may be absorbed *via* the bodily fluid canal. Carbon nanotubes square measure laden with antineoplastic medication and transported to lymphatic system to eradicate pathological process growth cells by discharging the medication. Ji *et al.* effectively transported gemcitabine to bodily fluid nodes with extreme certainty by utilizing a bodily fluid targeted drug delivery system depends upon magnetic MWCTs [175, 176].

After general administration into animals, bio-distribution of carbon nanotubes may be a hugely important thought. In recent times, several scientists saccomplished *in-vivo* bio-distribution

and pharmacokinetic studies. Distinct nanotube materials are utilized bythem, such as surface functionalization's ways and pursuit methodologies [177]. The result showed sharp carbon nanotube uptake in reticuloendothelial systems (RES) organs like lungs, liver, and spleen within the absence of observable excretion in twenty-eight days [178]. In the medical analysis of carbon nanotubes, biodegradability and elimination may be thought to be one of the sizable obstacles that will cause hindrance. In a very current study denote via Alidori *et al*., SWNTs functionalized the usage of one, 3-dipolar cycloaddition. These nanotubes have been administered intravenously to the cynomolgus monkey (non-human primates). The injected SWNTs showed a biodistribution profile and prompt renal removal likewise to those detected in mice [179]. Even with such promising outcomes, clinical investigations of carbon nanotubes' capability as drug delivery carriers wouldn't be possible before their safety, biodegradation, and elimination square measure unquestionable.

Toxicity: The toxicity of carbon nanotubes concerning healthy cells and tissues is that the foremost subject is carbon nanotubes' bio-medical utility. As a matter of reality, there are numerous factors on that the toxicity of carbon nanotubes depends, at the side of however not restricted to, form and size of carbon nanotubes, surface modification, concentration, mode of administration, physical and chemical elements interactivity, and responsiveness of the organism 180,181.

As an example, the toxicity of multi-walled carbon nanotubes having 3 separate diameters for epithelium cells of vena in a human was studied by Zhao *et al.* 182. It had been once disclosed that carbon nanotubes with minimum diameter elicited an extensively bigger stage of toxicity than the various forms of carbon nanotubes. Induction of protein unleashes of high level, intracellular reactive oxygen species, monocyte adhesion, and DNA damage.The toxicity of carbon nanotubes has an impression on the pulmonic system is one among the essential a part of the analysis [183, 184]. The inflammation of respiratory organ tissues will occur as a consequence of carbon nanotubes being an area of respirable substances. Regular inflammation and respiratory organ harm can even open the means for pulmonic pathology and carcinoma [185]. An area of analysis has discovered that even a tiny, low fraction of carbon nanotubes will cause inflammation of the lungs in animals [186]. When inflammation, it further showed that carbon nanotubes even have the flexibility to induce modulation of respiratory organ cell proliferation as a consequence of pulmonic fibrosis, direct injury, factor harm, and metabolic process cancer. At the side of the system respiratorium, it has demonstrated that carbon nanotubes will show toxicity on alternative organ systems and organs as well that embrace the nervous system, generative system, liver, and kidneys [187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198].

In a contrary manner, despite antecedently declared information on the hepatotoxic effects of carbon nanotubes, there's a series of reports showing minor or lack hepatotoxic effects of carbon nanotubes [199, 200]. For instance, it's been discovered that spermatozoon viability stays unaffected by the use of reduced graphene oxide and single-walled carbon nanotubes, and these nanotubes don't hinder the spermatozoon sorting technique [201]. The outcomes of some other analyses incontestable that carboxylated and hydroxylated multi-walled carbon nanotubes will cause moderate toxicity on human umbilical vein endothelium cells [202]. Lim *et al.* discovered that there's a scarcity of teratogenicity of multi-walled carbon nanotubes in rats [203]. Hence, the study of toxicity, teratogenicity, and carcinogenicity of carbon nanotubes is open and its obscurity close to the conclusion.

CONCLUSION: Nanotechnology has persuasively opted for medication and biotechnology in current years. In the past decade, the distinctive physical properties of carbon nanotubes triggered a broad analysis of nanoscale devices for varied uses in treating cancer. The unconventional one-dimensional configuration and tuneable length of carbon nanotubes turned into the best platform to analyze dimensions and kind effects *in-vitro*, even more significantly *in-vivo*. There square measure two classes of carbon nanotubes. These nanomaterials turned out to be functionalized by victimization valence and no covalent bonding. In the drug delivery system, functionalized carbon nanotubes are utilized as nano-carriers.

Carbon nanotubes merely exhibit completely different intrinsic physical properties that resonate with resonance photoluminescence, robust NIR optical absorption and Raman scattering. Further, these properties may be utilized to perform varied functions like static and functional imaging, passive and active pursuit, drug and factor vectoring, and targeting. Nearly all of the higher than mentioned capabilities of carbon nanotubes can be combined on an individual nanotube and developing them a promising platform for the treatment of multimodality cancer and imaging. Carbon will besides be utilized with conventional cancer medical care like radio medical care and chemo medical care. In cancer treatment, carbon nanotubes additionally seemingly transport antineoplastic medication to the targeted space. These Nanocarriers also are applicable in factor medical care. The chemistry parameters of carbon nanotubes play a key role within the pharmacological medicine, metabolism, and toxicity of carbon nanotubes. Within the medical specialty applications, well-functionalized carbon nanotubes are favourableby each technique, covalent and non-covalent bonding. PEGylation might additionally be the simplest methodology to spice up the in vivo behaviours of carbon nanotubes. Systematic analysis of the long-lasting toxicity of carbon nanotubes exposure is effective of exclusive thought in future analysis.

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