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Carbon nanoparticles: A new frontier in targeted cancer chemotherapy

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Abstract
The integration of carbon nanoparticles (CNPs) in cancer chemotherapy has opened new avenues for enhancing the efficacy and specificity of cancer treatments. Carbon-based nanomaterials, including carbon nanotubes, graphene, and carbon dots, exhibit unique properties such as high surface area, biocompatibility, and the ability to be functionalized with various therapeutic agents. These properties enable CNPs to serve as efficient drug delivery systems, targeting cancer cells while minimizing damage to healthy tissues. Recent advancements have demonstrated the potential of CNPs in overcoming multidrug resistance, enhancing drug solubility, and providing controlled drug release. This review explores the application of carbon nanoparticles in cancer chemotherapy, highlighting their impact on treatment outcomes and the challenges that remain in translating these findings to clinical practice. The promising results underscore the need for further research to fully harness the potential of CNPs in revolutionizing cancer therapy.

Keywords: Carbon nanoparticles, Cancer chemotherapy, Carbon Nanotubes, Fullerene, Graphene

I. Introduction

Cancer can be realized as an autonomous disease with genetic roots that is driven by the unchecked growth of malignant cells. The disease's ability to take advantage of the host's physiological functions determines how far it can spread.[1] It is a deadly age-related pathology that ranks among the most horrible illnesses. The efficacy of conventional therapy methods, such as surgery, chemotherapy, and radiotherapy, has not been effective cure.[2] Moreover, they frequently result in treatment failure and have serious negative effects on the body's physiological processes. If the tumour is found early enough, it can be surgically removed with precision in medicine; if it spreads, treatment is frequently challenging, expensive, and largely ineffective. Therefore, to enhance the effectiveness of treatment, it is imperative to develop new intelligent medications in addition to innovative therapeutic approaches. The most recent approach for managing and diagnosing cancer is nanotechnology, which creates a new therapeutic drug delivery option for the treatment of cancer.[3] Nanoparticles (NPs) have a few benefits over other traditional chemotherapeutic drug delivery methods.[2]

Cancer originates from a cell of the body. To maintain the body's homeostasis and steady-state, healthy cells divide and create new ones to replace the old ones. However, if a cell's genetic material is mutated, the cells may grow abnormally and eventually form a tumour.[3] Chemotherapy, surgery, radiation therapy, and immunotherapy are some cancer treatment options. Although chemotherapy is the most effective treatment for metastatic tumours, many side effects have been reported, the most serious of which are toxic side effects, damage to healthy cells, and tumour recurrence.[4] Furthermore, the ability of cancer cells to become resistant to multiple drugs at the same time – a trait known as multidrug resistance remains a significant impediment to successful chemotherapy. Another important limitation of conventional chemotherapy is its lack of specificity, which results in low concentrations of chemotherapeutic drugs at tumour sites. As a result, cancer research aims to develop treatments that reduce these negative side effects, progressing to the most promising cutting-edge therapies, such as gene therapy and nanomedicine.[28]

The field of science is interested in carbon nanomaterials (CNMs) because of their versatile functionalization chemistry, electronic, optical, thermal, and mechanical properties. Additionally, CNMs appear to be safer and more biocompatible than metal-based nanomaterials when used in cancer therapeutics.[6] Because they are smaller, have a larger surface area, are more precisely designed for surface properties, are more reactive, and have unique optical properties, nanomaterials can combine imaging and targeting onto a single nanoscale platform. These properties set them apart from bulk materials. Nanomaterials are widely available, and their physiochemical characteristics can be precisely engineered to satisfy the unique requirements of adjusting the TME to boost the effectiveness of cancer therapy. Carbon nanomaterials are employed in a variety of biological and biomedical applications, including advanced cancer treatment.[7]

Because of the enhanced permeability and retention (EPR) effect of tumours, nanotechnology systems have clear advantages in the treatment of cancer. To begin with, these systems can accumulate

at tumour sites much more than they can in normal tissues.[5] Larger pore sizes in blood vessels feeding tumour tissues than in healthy tissue led to preferential tumour accumulation of anticancer drugs at the nanoscale, improved treatment efficacy, and decreased systemic toxicity. Nanomaterials are also being used as thermal nano-scalpels for the ablation of cancer cells, by taking advantage of their superior optical and electromagnetic properties. Their ability to target tumorous tissue specifically through surface functionalization increases their therapeutic potential and decreases their side effects.[8]

Targeted drug delivery has been a hot topic in research for over a decade, and for good reason when given systematically, phagocytic cells and renal excretion often compete with the tumour for nanoparticles. Because of their large surface area, nano-DDSs are highly effective at loading and releasing chemotherapeutic drugs.[18] They may be made to have higher pharmacokinetic and bioavailability, which could improve cancer targeting and extend the time that a drug circulates in a systematic manner. Because of their special physicochemical qualities, Carbon nanoparticles are now widely used in cancer treatment. With the potential to deliver medications to cancerous cells, they are regarded as one of the most promising nanomaterials.[22] They have also been utilized in gene therapy and lymphatic targeted chemotherapy. Carbon's covalent bonds with oxygen, hydrogen, and nitrogen provide simple pathways for organic or biological molecules to functionalize carbon surfaces. Additionally, their potent near-infrared (NIR) optical absorbance is helpful for photothermal tumour ablation. Their capacity to release heat in a radiofrequency field can be utilized to cause thermal cytotoxicity in cancerous cells. Consequently, photothermal and photodynamic therapy can be applied to them.[9]

This review emphasizes the characterization of specific types of carbon nanomaterials and their application as anticancer drug delivery system.

1. Nanoparticles

Nanoparticles are spherical polymeric particles that are composed of natural or synthetic polymers. They range in size from 10 to 500 nm. Because of their spherical shape and large surface area to volume ratio, these particles have a wide range of potential applications. [1,3] Nanoparticle technology is rapidly evolving, resulting in novel and effective treatments for a variety of diseases, including neurodegenerative diseases such as Alzheimer's and Parkinson's.[10] Nanoparticles can be classified into one of several types based on their size, shape, and material characteristics. Some classifications differentiate between organic and inorganic nanoparticles; the former includes dendrimers, liposomes, and polymeric nanoparticles, whereas the latter includes fullerenes, quantum dots, and gold nanoparticles.[11] Other classifications of nanoparticles include carbon-based, ceramic, semiconducting, and polymeric. Furthermore, nanoparticles can be hard (e.g., titania [titanium dioxide], silica [silica dioxide] particles, and fullerenes) or soft (e.g., liposomes, vesicles, nanodroplets).[28]

1.1. Types of Nanoparticles

1.1.1. Inorganic nanoparticles

Inorganic nanoparticles are biocompatible and more stable than organic materials. These NPs include quantum dots, metallic nanoparticles, polymers, and porous nanomaterials, the latter of which is primarily composed of silica materials. Inorganic nanoparticles (NPs) typically have an inorganic core and an organic shell for targeted drug delivery.

1.1.2. Quantum Dots (QDs)

Inorganic materials with semiconducting qualities, known as quantum dots (QDs), are typically created using elements from the periodic table II–VI or III–V. Their radius typically ranges from 10 to 100 Å. Because of their crystalline metalloid core structure and composition as well as quantum-size confinement which happens when metal and semiconductor particles (QD cores) are smaller than their Bohr radii (1–5 nm), which enables them to have semiconductor properties-QDs have unique physicochemical properties.[14]

1.1.3. Metallic Nanoparticles

Metal oxides or a metallic core structure covered in an organic material are common forms of metallic nanoparticles, or metallic NPs, with a typical diameter of 1-100 nm. These particles have fascinating chemical and physical characteristics that could be used to treat cancer.[18] These systems have several benefits, including easy synthesis, a large surface-area-to-volume ratio, magnetic properties for some iron-based particles, and a functional surface that may increase their affinity and selectivity to target molecules. The metallic nanoparticles' surface can be readily modified to engage in H-bond, covalent, and electrostatic interactions with other molecules and targeting agents. Significantly, and pertinent to their clinical use, the metallic NPs show improved stability and half-life in distribution, biodistribution, and targeted specific targeting into the target site.[14]

1.1.4. Inorganic Porous Nanoparticles

Inorganic porous nanomaterials have been identified as promising drug carriers due to their unique structural properties, such as high

biomolecule loading capacity, the ability to modify the surface, and the controllable release of drug molecules. This is because of their porous solid structure, with particle units creating uniform pores ranging from microporous to mesoporous.[12]

1.1.5. Magnetic Nanoparticles

Magnetic nanoparticles (NPs) are being studied for cancer therapy due to their potential for targeted drug delivery. These particles are appealing because they generate more heat under microwave irradiation, which allows the loaded drug to be released more easily. Magnetic drug delivery is a non-phagocyte-eliminating system that allows for long-term circulation. Peptides and polymers in the particle's outer shell can combine to acquire this feature.[14] Magnetic-based technologies use external magnetic fields to guide drug delivery in vivo and in vitro through functionalized nanoparticle surfaces. Superparamagnetic nanoparticles are the preferred choice for such applications.[18]

1.1.6. Carbon Nanoparticles

Carbon nanoparticles are made by using the element carbon. These nanoparticles have unique physical and chemical properties that make them promising for medical applications.[13] Their ability to penetrate cell membranes and electron hybridization of carbon atoms make them ideal for functionalization or loading with therapeutic compounds. Carbon NPs consist of various carbon compounds, including graphene, graphene nanotubes, and fullerenes, each with distinct properties. Some of them have also been applied successfully in cancer therapy applications.

1.1.7. Organic Nanoparticles

Organic nanoparticles are tiny particles made up of combined molecules or polymers. These materials are of great interest because of their ease of fabrication and the wide variety of combined structures they can achieve. They typically range in size from 1 to 100 nanometre (nm). However, their size is comparable to biomolecules, making them useful in a variety of fields, including biomedical sciences and nanotechnology.[15]

Although inorganic nanoparticles have received a lot of attention in the field of cancer therapy, their toxicity and limitations for safe in vivo use have generated a lot of interest in study of organic, biocompatible nanoparticles for various cancer treatment applications.[12] Organic nanoparticles are developed in such a way that they are nontoxic to cells, biodegradable, and do not cause cellular or tissue damage.

2. Carbon Nanoparticles as therapeutic tool for cancer

Carbon exists in various allotropes, including diamond (sp3 bonds) and graphite (sp2 bonds). Carbon-based materials' electrical, mechanical, optical, and thermal properties have attracted attention in biomedical fields like biological sensing, delivery of drugs, tissue engineering, and target-specific therapeutics. Carbon nanotubes, fullerenes, and graphene are three of the various types of CNPs that are most frequently used in the biomedical industry.[19] In their purest forms, carbon nanoparticles have a high surface area made up of sp2-bonded carbon atoms, which makes them extremely hydrophobic.[14]

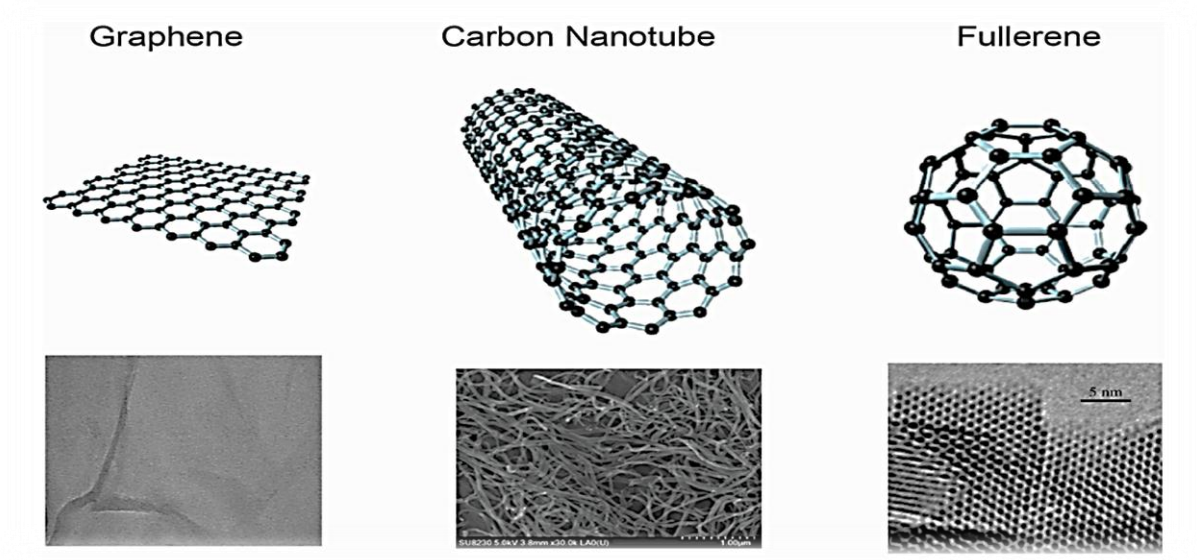

Figure 1: Carbon nanoparticles. 2D diagrams and electron microscope pictures of graphene, carbon nanotubes and fullerene.[1]

2.1. Graphene

The unique two-dimensional honeycomb crystal lattice that makes up graphene is made up of a single layer of carbon atoms bound together by space bonds. Its broad surface area availability, variety of functional groups, and ease of preparation make graphene oxide, a derivative, a popular choice for biomedical applications.[2] A component of the graphite crystal structure, graphene was only thought to exist until its layers were found and separated from graphite crystals. Once this happened, it was demonstrated to possess special electrical, optical, chemical, and mechanical properties. Because of their planar structure, high concentration of delocalized pi electrons, availability of functional groups like hydroxyl and carboxyl groups, and epoxy bridges, GO sheets have an exceptional capacity to immobilize a wide range of materials, including medications and fluorophores for medical applications.[1] In recent times, graphene sheet characteristics have begun to challenge CNT dominance in potential biomedical applications. Graphene's, especially in their PEGylated forms, have been shown to have lower in vitro cytotoxicity than CNTs.

Because of graphene's large surface area, there are excess electrons available for pi stacking interactions, which some aromatic anti-cancer medications, such as doxorubicin and camptothecin, can form. The hydroxyl and carboxyl groups of the GO and the amine groups on the drug form a hydrogen bond, which is found to be dependent on the pH of the surrounding environment as well as the loading capacity and release of these anti-cancer drugs.[7] Two suggested pathways of internalization are energy-dependent endocytosis or phagocytosis after the drug has been administered and delivered to the intended cell, and energy-independent direct penetration. Because GO-based nanoparticles exhibit lower cytotoxicity in cells than CNT-based nanoparticles do, some speculate that GO-based nanoparticles can only enter cells through energy-dependent endocytosis. To further promote specificity in drug delivery and reduce the possibility of cytotoxic adverse effects on non-cancerous cells, targeting moieties particular to the tumours may also be designed onto the surface of the GO-nanoparticles.[2]

2.2. Carbon Nanotubes (CNTs)

Carbon graphitic nanotubes (CNTs) are hollow, well-ordered carbon graphitic nanomaterials with cylindrical structures made of graphene sheets rolled at precise angles.[1] CNTs are seamless cylindrical tubes made of sp2-hybridized carbon atoms, like single or multilayered graphene. They have a high aspect ratio and can be as small as 1 nm in diameter and several micrometres in length. There are two types of carbon nanotubes: single-walled (SWCNTs) and multiwalled (MWCNTs). Due to CNTs' poor water solubility, various surface functionalization's and modifications have been used to improve their dispersibility and biocompatibility. Peroxidases may biologically degrade CNTs, implying that their use in biomedicine is feasible and safe.[7]

The rationale behind CNT-mediated drug delivery to tumour targets is comparable to that of other drug delivery methods involving nanoparticles. Two critical non-covalent interactions required for NP-drug binding are pi stacking and hydrophobic interactions, which are made possible by the aromatic rings of CNTs. Since these medications alone have a limited therapeutic window owing to systemic toxicity, CNTs can also be used as scaffolding to carry and target medications for greater therapeutic efficacy. Several classes of anticancer agents, such as topoisomerase inhibitors, anthracyclines (like doxorubicin), platinum-based medications (DNA chelators, like cisplatin and carboplatin), antimetabolites (which interfere with metabolic pathways during the formation of nucleic acids in cancer cells, including antifolates like methotrexate and purine/pyrimidine antagonists, like gemcitabine and 5-fluorouracil) and ant microtubules, have been loaded onto CNTs for targeted delivery. Upon reaching the tumour mass through either passive or active targeting, the CNT-drug complex becomes internalized and specific mechanisms are triggered to release the drug load.[17] Energy-dependent receptor-mediated endocytosis is one of the many mechanisms that have been suggested to explain this increased cellular uptake of CNTs. Diffusion or penetration are other passive, energy-independent ways that CNTs can internalize across a cell membrane. SWCNTs may also "pierce" the cell to pass through the membrane without using any energy because of their tiny size and needle-like shape. It has been proposed that CNT cytotoxicity is caused by penetration into the cell membrane through such piercing processes.[19] To completely comprehend the cytotoxic effects and internalization effects of carbon-based nanomaterials, additional investigation is required.

2.3. Fullerene

Fullerenes have hollow carbon groups made up of sp2 carbons arranged in a symmetrical cage that varies in size like a sphere. C60, one of the most prevalent fullerene forms, possesses 60 carbon atoms, 12 pentagons made of C5–C5 single bonds, and 12 hexagons made of C5–C6 double bonds.[1] Fullerenes, in contrast to graphene and carbon nanotubes, have a more uniform size distribution. Common fullerenes used in biomedical applications have sizes of less than 5 nm. While these

nanoparticles would gather passively at the microenvironment of tumours, they would also be quickly removed from the body by renal filtration and urine excretion, which could reduce their effectiveness.[7]

Different fullerene variations have also been developed for drug delivery-based cancer therapies. Fullerenes have been utilized for diagnosis. If fullerenes are functionalized effectively to be soluble in aqueous environments, their small sizes allow them to easily pass through cellular membranes without harming cells. Fullerenes internalization property makes them the ideal carrier for chemotherapeutic agents, increasing their therapeutic efficacy by allowing them to enter tumorigenic cells. The effectiveness of a variety of chemotherapeutic payloads, such as doxorubicin, paclitaxel, cisplatin, and even DNA-based gene therapies, loaded onto fullerenes has been assessed both in vitro and in vivo.[19]

3. The applications of Carbon Nanomaterials in the Treatment of Cancer

By using carbon nanomaterials in the treatment of cancer involves delivering medications or small therapeutic molecules to specific target sites, thermally ablating tumour cells, delivering genes and nucleic acids, theragnostic, and utilizing combined therapy approaches.

3.1. Carbon nanomaterials for anticancer delivery of drugs.

Therapeutic drug delivery has demonstrated a strong potential for CNT-based nano-vectors, particularly functionalized nanotubes. CNTs have been utilized as nanocarriers for anticancer medications, including doxorubicin (DOX), betulinic acid (BA), MTX, gemcitabine (GEM), etoposide, paclitaxel (PTX), chelerythrine, camptothecin (CPT), carboplatin, cisplatin (CIS), Pt (II), and Pt (IV), through suitable functionalization.[16] Presented hydrophilic mesoporous carbon nanoparticles as vehicles for the long-term release of camptothecin, a hydrophobic anti-cancer medication. Mesoporous silica was recently used to encase magnetic GO and magnetic CNTs for the loading and delivery of CPT. When compared to the pure medication, the combination of prepared nanomaterials and CPT showed a remarkably high level of cytotoxicity towards HeLa cell lines. Low doses of medication are used in CNT drug delivery, which is thought to have a high efficacy in cancer therapy.[23] The EPR effect of tumours causes nanoparticles to be retained longer in tumours than in normal tissues. The anatomical and pathological distinctions between solid tumours and normal tissues give rise to the unique phenomenon known as the EPR effect. Most solid tumours have greater vascular density (hypervascularity) than normal tissues and organs.[25] Numerous factors, such as the size, surface characteristics, and angiogenesis level of the tumour, influence the accumulation of nanoparticles in tumours. Anticancer medications based on nanocarriers have far greater activity than free medications when they accumulate in tumour tissue through the EPR effect.[20]

In addition to creating nanomaterials specifically targeted at tumour tissue without a highly selective semipermeable membrane barrier, drugs can also be delivered via nanoparticles that can pass through a variety of biological barriers. Because antineoplastics and some other drug types cannot pass through the blood-brain barrier (BBB), their effectiveness is severely limited. It seems highly promising to use nanoparticles to deliver across this barrier. It has been discovered that nanoparticles can pass through the blood-brain barrier (BBB) after hyperosmotic mannitol opens tight junctions.[21] This mechanism can also deliver therapeutic agents continuously to treat diseases that are challenging to treat, like brain tumours.

Drug delivery CNTs are widely used, however there are still some significant problems that need to be resolved. These include long-term cytotoxicity in the body, inconsistent size during synthesis, loading deviations for drug CNT complexes, and controllability of release at the target site. It is likely that carbon nanotubes (CNTs) will rank among the most effective cancer therapy tools if these challenges are resolved.

3.2. Carbon nanotubes as carriers of chemotherapy drugs

CNTs have potential as carriers for cancer therapy in addition to their use as mediators for photothermal and photodynamic therapies, which use combinations of light energy to directly destroy cancer cells without seriously harming healthy tissue. Furthermore, it was discovered that CNTs can readily penetrate a wide variety of cells, including yeast, bacterial, and mammalian cells. Because of their small size and high aspect ratios, carbon nanotubes (CNTs) have a high specific surface area due to their needle-like shapes, which allows them to conjugate or adsorb onto a variety of therapeutic molecules.[27] CNTs' needle-like morphology also makes it possible for target cells to internalize them.

CNTs are thought to be a promising class of nanocarriers for the administration of drugs. The delivery of antitumor agents, such as medications, plasmid DNA, genes or DNA, small-interfering RNA (siRNA), oligonucleotides, and DNA/RNA aptamers, has been extensively studied using carbon nanotubes (CNTs). Additionally, proteins, peptides, and immunotherapy components can be delivered by CNTs. [24]

Conjugated polymers, which are widely used for drug and delivery of genes, are among the many types of CNT that are used as drug, nucleic acid, and protein carriers. Polymers are essential to drug delivery technology because they allow for cyclic dosage, tuneable release of hydrophilic and hydrophobic drugs, and controlled release of therapeutic agents in constant doses over extended periods of time. They provide defence against deterioration by chemicals.[29] Certain polymeric systems that are nanoparticulate have the capacity to pass through the blood-brain barrier. Furthermore, smart polymers can react to changes in temperature, pressure, pH, and other atmospheric conditions, which makes them very useful for targeted drug delivery. Certain polymeric systems that are nanoparticulate have the capacity to pass through the blood-brain barrier. Furthermore, smart polymers can react to changes in temperature, pressure, pH, and other atmospheric conditions, which makes them very useful for targeted drug delivery.[26] Additionally, certain polymeric systems conjugated with biomarkers or antibodies aid in the specific molecular targets that are present in cancers. Thiolate PEG and Silica-PEG surface coatings increase photostability and water solubility. These are used to treat lymphoblastic leukaemia and prostate cancer on Caspar PEG intron. There are polymers that are nontoxic, biodegradable, and biocompatible. Because biodegradable polymers can break down inside the body into non-toxic monomers, they are frequently used in drug delivery.[30]

II. Conclusion

The clinical application of carbon nanoparticles (CNPs) in cancer chemotherapy marks a significant advancement in oncology. Their distinct properties, such as high surface area, biocompatibility, and functionalization capabilities, have shown great promise for improving drug delivery, overcoming multidrug resistance, and improving treatment specificity. While the preclinical results are promising, translating these findings into clinical practice necessitates addressing issues such as toxicity, long-term effects, and large-scale manufacturing. Continued research and development are required to fully realize CNPs' potential to revolutionize cancer therapy, providing hope for more effective and targeted treatments in the future.

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