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Review

Carbon-Based Nanomaterials for Delivery of Biologicals and Therapeutics: A Cutting-Edge Technology

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Abstract: After hydrogen and oxygen, carbon is the third most abundant component present in the cosmos with excellent characteristic features of binding to itself and nearly all elements. Since ancient times, carbon-based materials such as graphite, charcoal, and carbon black have been utilized for writing and drawing materials. As these materials possess excellent chemical, mechanical, electrical, and thermal features, they have been readily engineered into carbon-based nanomaterials (CNMs) such as carbon nanotubes, graphene oxide, graphene quantum dots, nanodiamonds, fullerenes, carbon nano-onions, and so forth. These materials are now widely explored in biomedical applications. Thus, the emergence of CNMs has opened up a gateway for the detection, delivery, and treatment of a multitude of diseases. They are being actively researched for applications within tissue engineering, as vaccine vectors, and for the delivery of therapeutics to the immune system. This review focuses on the recent advances in various types of CNMs, their fabrication techniques, and their application in the delivery of therapeutics both in vitro and in vivo. The review also focuses on the toxicity concern of the CNMs and the possible remedies to tackle the toxicity issues. Concluding remarks emphasize all the CNMs discussed in the review over their possible biomedical applications, while the future perspectives section discusses the approaches to bring CNMs into the mainstream of clinical trials and their therapeutic applications.

Keywords: carbon nanotubes; graphene oxide; graphene quantum dots; fullerenes; nanodiamonds; carbon nano-onions; drug delivery

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1. Introduction

Nanotechnology has offered to mankind various nano-enabled products or nanosystems, currently also serving various biomedical applications. These nano-constructs and assemblages with drugs, proteins, DNA/RNA, viruses, cellular lipid bilayers, cellular receptor sites, and antibodies (pivotal for immunology), are intricate in the arena of nanostructural scope [1]. Carbon-based nanomaterials (CNMs) could be considered as such a class of nanosystems, which have been explored for the delivery of therapeutics, biosensing, and bioimaging [2]. Of late, they have been pragmatic in applications such as regenerative medicine [3], cancer therapy, and theranostics [4] (Figure 1).

Carbon is one of the most interesting elements that possess extreme qualities of forming a wide range of structures with different properties. Carbon is conventionally available in allotropes [5] as "hard" diamond and "soft" graphite, where atoms are pure sp^2 or sp^3 hybrids organized in a hexagonal or cubic lattice; owing to the valance of carbon atoms, other allotropes such as zero-dimensional fullerenes [6] and carbon quantum

dots [7], one-dimensional carbon nanotubes [8], and two-dimensional graphene sheets [9] (Figures 2 and 3) have been discovered. Carbon nano-onions [10] (CNOs) are another type of CNMs that are gaining considerable academic and industrial interest for their pertinence in various biomedical extents.

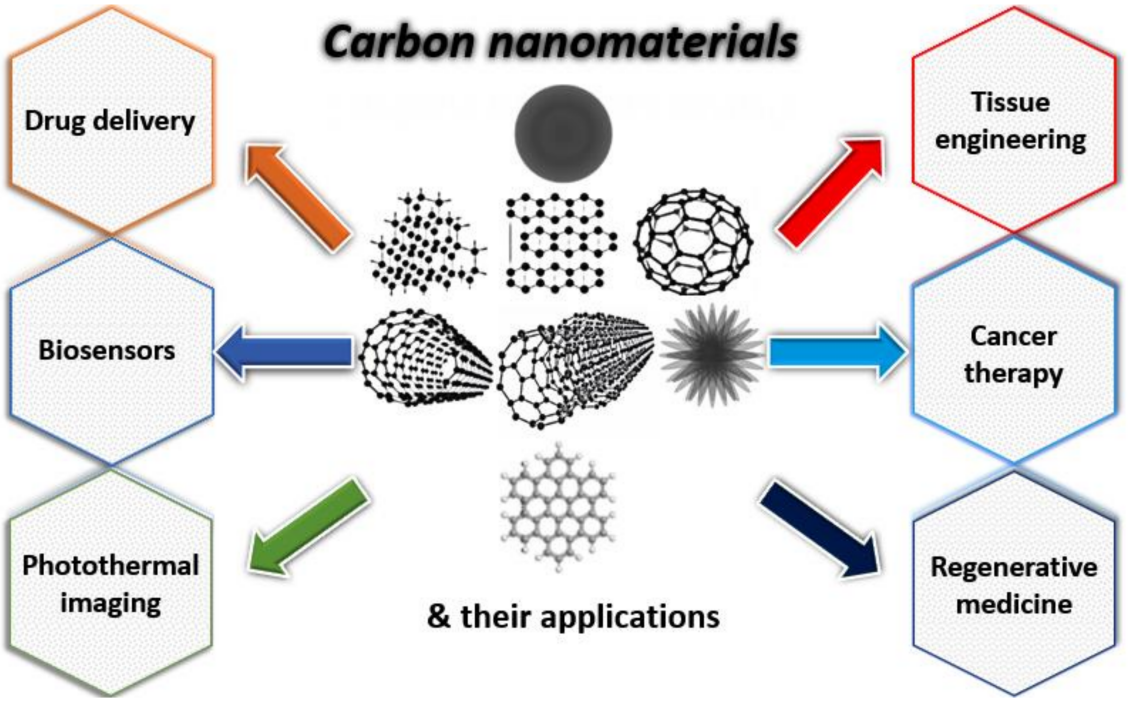

Figure 1. Carbon nanomaterials and their applications in the vast biomedical arena.

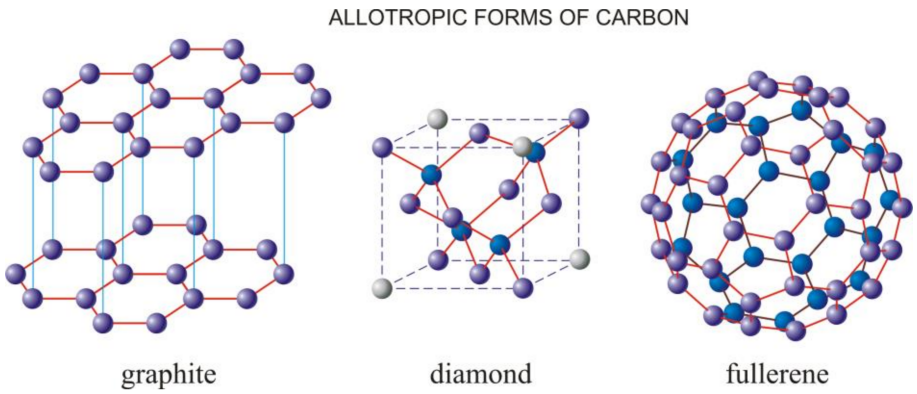

Figure 2. Various allotropes of carbon [11].

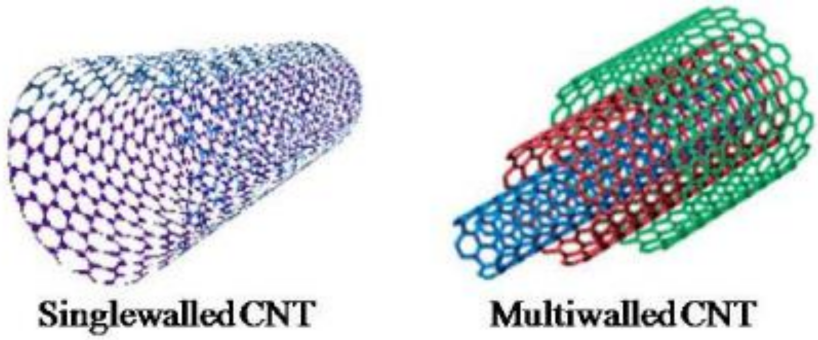

Figure 3. Single-walled and multiple-walled carbon nanotubes (CNT) [12].

Carbon nanomaterials possess specific properties such as high surface area, excellent mechanical and electrical properties that promote their application also in the therapeutic and diagnostic fields. A few of the advantages of carbon nanomaterials are summarized as follows, and Table 1 gives a brief overview of different CNMs discussed in this review with their benefits and limitations.

1. Their supramolecular π–π stacking attribute allows them to adsorb a high amount of drug.
2. As a result of their unique optical characteristics and facile amalgamation with luminous substances, CNMs can be utilized as theranostics materials.
3. CNMs possess excellent heat conversion capacity in the near-infrared region that could be well utilized for photothermal therapy.
4. Tuneable surface chemistry can be used for the controlled release of therapeutics.

Colloidal stability in the aqueous suspension of CNMs [13] is a major concern for their utilization in biomedical sectors; however, this can be tackled by activating the CNMs surface by covalent and non-covalent functionalization techniques. The functionalization of CNMs is one such unavoidable step that involves modification of the surface by introducing specific functional groups. Covalent functionalization approaches include oxidation, ozonolysis, plasma treatments, dehydrogenation, etc. [14].

CNMs have been exploited extensively in the delivery of therapeutics owing largely to the functionalization of their surface, rendering them capable of e.g., crossing biological membranes. Functionalization with appropriate targeting ligand aids in the reduction of cytotoxicity of loaded drugs toward healthy cells and augments therapeutic efficiency. The addition of small targeting molecules, e.g., folic acid [15,16] targeted against folate receptors expressed on the surface of a broad spectrum of solid tumor cells, ligands having affinity against a given receptor overexpressed on a specific tumor type [17], antibodies that identify tumor-associated antigens [18,19], and magnetic nanoparticles [16], can be associated with the drug-loaded CNMs. Via these methods, active targeting by receptor-mediated endocytosis or drug accumulation at the target site via an external magnetic field can be attained. Thus, functionalized CNMs have found applicability in the delivery of small molecules, peptides, proteins, and nucleic acids [20]. For instance, CNMs have been utilized in the delivery of anticancer agents [21], fluorescent markers for tumor detection [22], cancer phototherapy [23], theranostics [24], and so forth.

Table 1. A brief overview of carbon nano-onions (CNMs) with their advantages and limitations [25–29].

S. No.	Carbon-Based Nanomaterials	Advantages	Limitations in Biomedical Applications
1.	Carbon nanotubes	Has good mechanical strength, aspect ratio, conductivity, and chemical stability. Offers tunable physical properties (e.g., diameter, length, single-walled vs. multi-walled, surface functionalization, and chirality), biocompatibility, and high surface area.	Lack of solubility in aqueous media, non-homogenous in size (diameter and length), and possibilities of metallic impurities. Pristine CNTs being a lightweight powder may enter into the respiratory tract.
2.	Graphene/graphene oxide/graphene quantum dots	Offers excellent electrical, optical, and thermal properties. The two-dimensional atomic sheet structure of graphene enables more diverse electronic characteristics than CNTs.	Colloidal instability, lack of reproducibility, limited synthetic control, poor chemical stability in the biological environment, susceptibility to the oxidative environment.
3.	Fullerenes	Peculiar photoelectrochemical properties, the possibility of surface modification, and superconductivity.	Low aqueous solubility, accumulation in cell membranes, susceptible to degradation in the presence of light and oxygen, susceptible to deactivation process such as quenching.
4.	Nanodiamonds	Fluorescence and photoluminescence, biocompatible, smaller size compared to other CNMs, hard, corrosion-resistant, chemical inertness, high electrical resistance, and optical transparency.	Difficult to manufacture via covalent manner, tedious to remove toxic organic solvents while fabrication, abrupt drug release, and tendency to aggregate.
5.	Carbon nano-onions	Unique electronic and structural properties, including the ability to accept electrons reversibly, a high surface-area to volume ratio, and broad absorption bands.	Hydrophobic, low biocompatibility, aggregation, prone to oxidation, low surface chemical reactivity.

In this review, we are compiling the recent developments attained in the field of CNMs for the delivery of biologicals and therapeutics with an emphasis on carbon nanotubes, graphene oxides, graphene quantum dots, fullerenes, nanodiamonds, and carbon nano-onions as carrier materials. We have examined various CNMs employed for the treatment

of different dreadful ailments and discussed the toxicity concerns along with their possible remedial approaches. Their fate for clinical use in the upcoming future has also been a focus. We expect that this review will assist researchers to focus on the possible designing of CNMs for future biomedical implementations.

2. Carbon Nanotubes

Carbon nanotubes are cylindrical large molecules that are composed of a hexagonal arrangement of sp^2 hybridized carbon atoms (C–C distance of approximately 1.4 Å). The wall of CNTs comprises single or multiple layers of graphene sheets. The single-rolled sheets of graphene are termed single single-walled carbon nanotubes (SWCNTs), while multi-walled carbon nanotubes (MWCNTs) are formed by the rolling of more than one graphene sheet. Both SWCNTs and MWCNTs are capped at both ends of the tubes in a hemispherical arrangement of carbon networks known as the fullerenes warped up by the graphene sheet (Figure 4). The graphene layers of MWCNTs are separated internally by 0.34 nm on average, which constructs an individual tube of a larger outer diameter of 2.5 to 100 nm, while SWCNTs have the diameter in the range of 0.6 to 2.4 nm only. Single-walled CNTs own a well-defined wall structure in comparison to multi-walled CNTs, which have slight structural defects displaying somewhat unstable nanostructure. CNTs with their small size, high surface area to volume ratio, and ability to contain biomolecules renders them ideal candidates for the delivery of various substances [30].

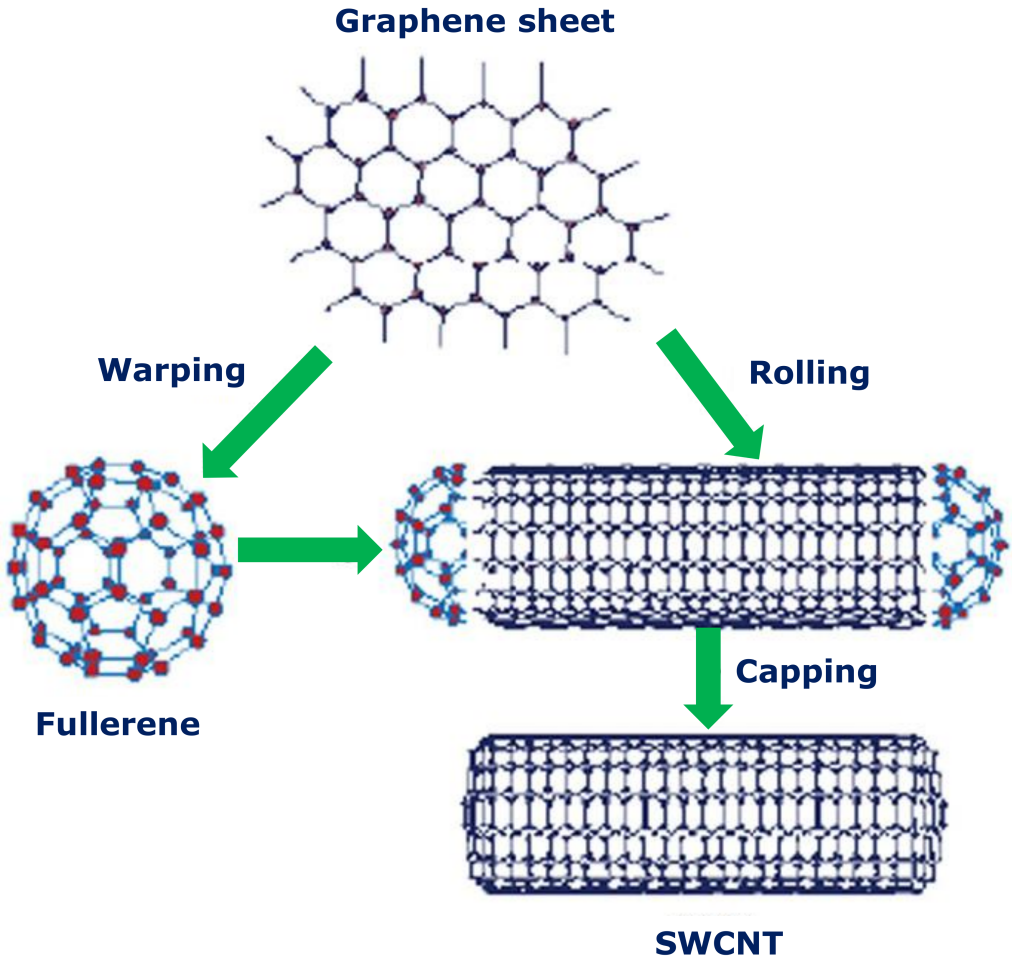

Figure 4. Preparation method of end-capped single single-walled carbon nanotubes (SWCNTs) [30].

Carbon nanotubes have found enormous potential due to their size (1–100 nm) which can be considered 1000 times thinner than human hair; still, they are 50 times sturdier than steel. Carbon nanotubes possess exclusive spectroscopic properties, their end and sidewalls

can be easily functionalized either covalently or non-covalently, and they can be fabricated with bioactive peptides, small-molecule drugs, proteins, or nucleic acids [31]. Such agents can be easily conjugated to the nanotube through a cleavable bond. CNTs possess the potential for penetrating the cells, which enhances the cellular uptake of therapeutic agents and protects them during transportation and cellular permeation. The recent advancements made in the carbon nanotube-based delivery of various therapeutic agents are summarized in Table 2.

Drug loading to the end-capped CNTs can be attained during the synthesis or post-synthesis of the CNTs. Drug loading largely depends upon the melting point, reactiveness, surface tension, and sensitivity of the molecules to be inserted and the diameter of the CNTs. After synthesis, drug loading can be achieved by opening up the ends of the CNTs by passing electric currents through them, or by attacking the CNT with acid that corrodes the angled end parts of the tube, or by oxidization using carbon dioxide [32,33]. The most appropriate method of drug loading is the attachment of a functional group to the CNTs [34]. The functional groups can be either bonded inside or outside of the walls. Gao et al. reported that hydrophobic and van der Waals forces also play an important part in aqueous solutions during drug loading [35]. After loading, CNTs are washed using a solution that dissolves the deposits left on the outer surface [36]. Post drug loading, the caps are closed by passing a current that fuses the ends [37]. Drug loading during synthesis yields low loading efficiency of around 10% whereas, after synthesis, the drug loading percentage can reach up to 50–100% [38].

Table 2. Recent advancement in carbon nanotube-based delivery.

S. No.	Indication	Drug/Vaccines/*Genes*	CNT Functionalization	Results	References
1.	Cell proliferation	Tissue engineering	Hydrogels of PEG-CNTs	Pristine CNTs and PEG-CNT hydrogels enhanced the cytocompatibility, viability, and proliferation of L29 fibroblasts.	[39]
2.	Cancer	Gemcitabine–Lentinan	MWCNTs/Gemcitabine (Ge)/Lentinan-Le	MWCNTs-Ge-Le showed augmented chemo and near IR-photothermal synergistic antitumor activity.	[40]
3.	Ischemic brain tissue	Dexamethasone	PEGylated vertically aligned MWCNTs	Low cytotoxicity was observed on the PC-12 cell line by the MWCNTs.	[41]
4.	Bladder cancer	Epirubicin (Epi)	Magnetic MWCNTs-Epi	Externally magnetic guided MWCNTs showed enhanced sustained release, prolonged retention behavior, and better antitumor activity than the free epirubicin both in vitro and in vivo.	[42]
5.	Antileishmanial	Cisplatin (Ci)	Ci-SWCNTs, Ci-MWCNTs	Ci-MWCNTs showed potent in vitro antileishmanial activity at low concentrations on *Leishmania. major*.	[43]
6.	Antibacterial activity	Curcumin	Glucose-modified calcium alginate single-walled carbon nanotubes (CA/SWCNT-Gl)	CA/SWCNT-Gl nanocomposite showed better antibacterial activity against *Bacillus cereus* and *Escherichia coli*.	[44]
7.	Cancer therapy	Doxorubicin (DOX)	N-isopropyl acrylamide carbon nanotubes loaded with DOX	Smaller polymer chain length resulted in more hydrogen bonding with the drug, five mer N-isopropyl acrylamide augmented DOX loading.	[45]
8.	Cancer therapy	Doxorubicin	A pH-sensitive conjugate of DOX-loaded SWCNTs and MWCNTs	Bonds between DOX and MWCNTs were stronger, which resulted in controlled drug release in cancer tissues in comparison to SWCNTs.	[46]
9.	Genetic engineering	Plastid genome	Chitosan complexed SWCNTs utilizing the lipid exchange envelope penetration mechanism	Chitosan–SWCNTs selectively delivered plasmid DNA to the chloroplast in *Eruca sativa*, *Nasturtum officinale*, *Nicotiana tabacum*, and *Soiacia oleracea*, and isolated *Arabidopsos thaliana* mesophyll protoplasts.	[47]
10.	Peptide delivery	G_S-protein	The casing of SWNTs with polycationic and amphiphilic peptides [H-(-Lys-Trp-Lys-Gly-)7-OH]	Seven times more uptake in comparison with the SWCNT–peptide composite without PEGylation.	[48]

2.1. Techniques for the Fabrication of Carbon Nanotubes

Carbon nanotubes can be produced by various innovative methods such as arc discharge, laser ablation (excluding carbon black), and chemical vapor deposition methods (Figure 5). The detailed fabrication methods of CNTs have already been extensively reviewed [49,50]. Also, the types and properties of these nanomaterials can be manipulated

by altering fabrication conditions such as reaction temperature, input gas concentration, or pressure [51].

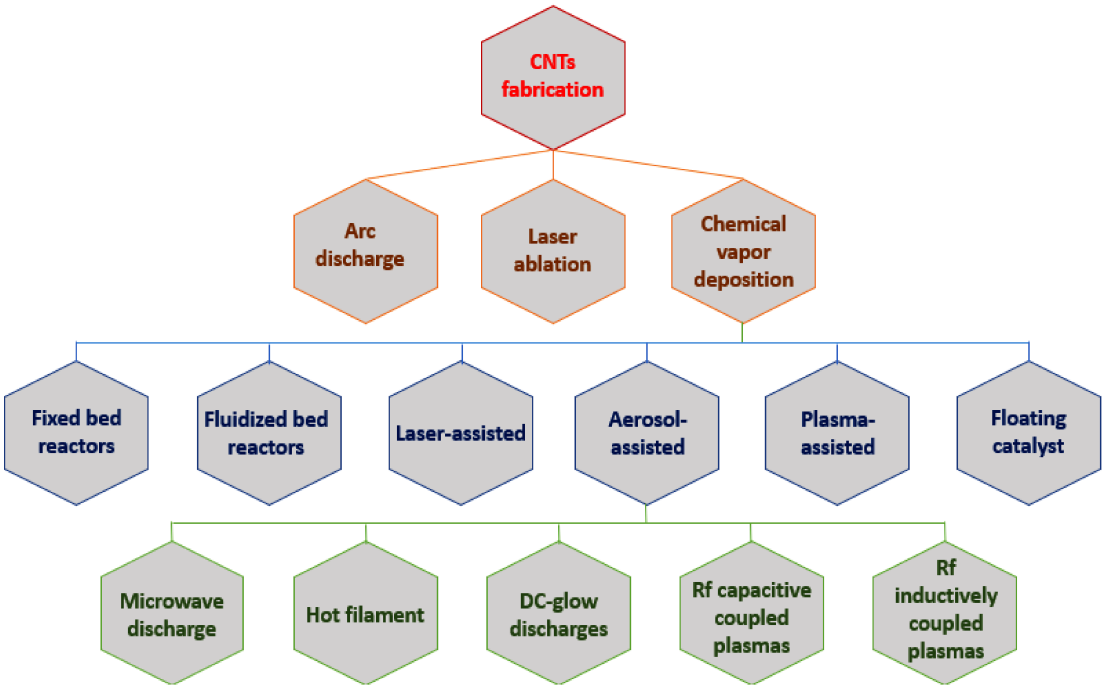

Figure 5. Fabrication methods of carbon nanotubes. Adapted from [49].

2.2. Functionalization of Carbon Nanotubes

As a result of their innate hydrophobic nature, carbon nanomaterials are very difficult to disperse in the aqueous phase. Therefore, to augment their solubility and amalgamation with the biological environment [52], their surfaces are usually functionalized non-covalently with amphiphilic macromolecules such as lipids, polymers, and surfactants or covalently with hydrophilic functional groups [49,53].

I. Covalent functionalization: Covalent modifications can be achieved by the direct sidewall functionalization or by defect group functionalization, which involves converting or rehybridization of sp^2 carbon into sp^3 configurations and finally forming covalency with attacking species [54]. This is either accomplished by using halogenation, the cycloaddition of azomethine ylides, and by the addition of radicals. The defect group surface modifications are finished by engendering defects by oxidation to yield carboxylic acid functionalities, which render them the functionality to attach various targeting groups such as peptides, proteins, or antibodies by employing amidation or esterification. Double and triple covalent functionalization is used for the fabrication of multifunctional CNTs that can be utilized for drug delivery. The double covalent functionalization can be achieved either by 1,3-dipolar cycloaddition and esterification/amidation and cyclopropanation; double arylation; arylation and amidation; amidation and cyclopropanation; double 1,3-dipolar cycloaddition; 1,3-dipolar cycloaddition and arylation; etc. The triple functionalization can be accomplished by simultaneous functionalization with different aryl diazonium salts [55,56].

II. Non-covalent functionalization: The covalent functionalization achieved by the aforesaid modifications may lead to the loss of electrical and optical characteristics of carbon nanomaterials. Therefore, non-covalent functionalization methods were used that can avert the negative effects of the covalent modifications of CNTs. Non-covalent functionalization can be done by adsorption/wrapping biopolymers, surfactants, and polymers on the tubular surface via π–π stacking and van der Waals interactions. Polymers—for example, polyethylene glycol (PEG), poly(vinylpyrrolidone), tetraalky-

lammonium, poly (meta phenylene vinylene), etc.—are utilized to form a case around the single-walled carbon nanotubes when suspended in a solution of the polymer. Surfactants such as sodium dodecyl sulfate, sodium dodecylbenzene sulfonate (SDBS), Triton X-100, etc., aid in the improvement of dispersibility, solubility, and permeability through gastrointestinal tract (GIT) by adsorbing on the surface of CNTs via π interactions [57,58].

2.3. CNTs for Drug Delivery

In the early 1990s, Ijima [59] developed a new allotrope of carbon using the carbon arc discharge method and named it the "multi-walled carbon nanotubes", which was needle-like and made up of several graphene sheets. A few years later, Prof. Ijima and Bethune established single-walled carbon nanotubes [60]. Both single and multi-walled carbon nanotubes hold exclusive mechanical, electrical, and structural properties which lends them higher forte, litheness, and electrical conductivity toward various biological entities that can be utilized for sensing, diagnosis, and drug delivery [61–63].

CNTs have unique electronic properties that are regulated by the quantum confinement of electrons, which propagates the electrons along the tube axis in the forward and backward direction, thus conserving energy and momentum. In addition, CNTs have a smooth density of states (DoS) and are characterized by several van Hove singularities [64]. This DoS relies on the diameter and chirality of the nanotube [65]. The conducting asset of CNT is an inverse function of its diameter; i.e., the bandgap between the valence and conduction bands decreases with an increase in diameter. At a definite point, both the bands overlap to give rise to metallic nanotubes.

Pristine CNTs are generally hydrophobic, having poor aqueous and organic solubility, and this hydrophobicity can be attributed to the size, structure, and bundling effect that restricts the uptake and assimilation in the biological environment [66]. Functionalization reduces this bundling effect that occurs due to the van der Waals forces between the adjacent nanotube surfaces, which aids in enhancing the biocompatibility and thus helps in cellular internalization and movement. Few studies reported that the functionalized nanotubes displayed improved biocompatibility with diminished in vivo and in vitro toxicity [67,68]. The extent of functionalization relies on the behavioral characteristics and reactivity of sidewall (curvature), the number of functional groups that can be attached to the sidewall, and steric hindrance between the functional groups and nanotube sidewall [69]. Drug entities can be attached to the functionalized CNTs sidewalls through covalent or non-covalent bonding.

Saikia N and Deka RC, in their studies, developed armchair (n, m) and zigzag (n, 0) SWCNTs loaded with 2-methyl heptyl isonicotinate and pyrazinamide, which were functionalized with PEG, and they investigated the structure, electronic properties, and reactivity of a series of 1,3-dipolar cycloaddition (DC) using first-principles density functional theory (DFT) calculations. The researchers reported that with an increase in sidewall functionalization, the hardness, and highest occupied molecular orbital-lowest occupied molecular orbital HOMO–LUMO energy gap decreases, which indicates a decline in the stability of the complex and localized deformation in the nanotube at the site of covalent attachment. They further reported that the solubility of pure isoniazid and pyrazinamide increased in the presence of SWCNTs. The researchers finally concluded that the optimum length and chirality of the CNTs is essential to comprehend the electronic characteristics of functionalized CNTs to understand the mechanism of the delivery of drugs [69,70].

Kang et al. tested the effect of temperature on the bovine serum albumin (BSA) release from chitosan-functionalized CNT with a thermosensitive polymer, poly-N-isopropyl acrylamide (NIPAAm) and 1-butyl-3-vinyl imidazolium (NIPAAm-co-BVIm). They reported that the release of BSA occurred just above the lower critical solution temperature of polyVBIm (38–40 °C) [71]. Functionalized CNTs lead to PEGylation, which improves constancy in the body fluids [72]. Both hydrophilic and hydrophobic drug material can be conjugated with the PEGylated CNTs either on the terminal functional groups of CNTs or to the PEG chains. Prakash Chandra et al. fabricated thermally stable, highly electrically

conducting polyaniline MWCNTs (PANI/MWCNT) nanocomposites doped in two different protonic acids (i.e., hydrochloric acid and sulfuric acid) by surfactant-assisted, in situ oxidative polymerization of aniline in the incidence of potassium persulfate as oxidant. The micellar structure of the surfactant abetted the dispersion of MWCNTs along with the development of PANI/MWCNT tubular structures and provided exceptional electrical and dielectric assets for microelectronic bids [73]. Shi et al. demonstrated ibuprofen release from a hybrid hydrogel composed of sodium alginate, bacterial cellulose, and MWCNTs using an electric field [74].

A dual-responsive drug delivery system was fabricated by Seyfoori et al. for the precise delivery of doxorubicin using MWCNTs functionalized with $MeFe_2O_4$ magnetic nanoparticles, which were coated with chitosan nanogel. The pH-responsive accelerated drug release was tested on U-87 glioblastoma cells, and the result suggested higher cell mortality in a time-dependent manner [75]. Meherjuoi et al. designed silver (Ag) nanowires as a stimulator for the release of cisplatin from the interior of the various types of CNTs. They compared CNTs, silicon carbide nanotubes, and boron nitride nanotubes and reported that the drug release was fast and not dependent on the structural composition of nanotubes [76].

Gutiérrez-Hernández et al. fabricated functionalized MWCNTs in combination with bacterial cellulose as a three-dimensional (3D) scaffold for osteoblastic cell culture. They mixed the MWCNTs with innate bacterial cellulose (secreted by *Glucanocetobacter xylinus*) to strengthen the mechanical properties of the bacterial cellulose. It was reported that the BC-MWCNTs scaffold reinforced osteoblast viability, adhesion, and propagation at higher levels in comparison to traditional culture substrates. Finally, they concluded that the BC-MWCNTs scaffold holds the potential for bone regeneration [77].

Chemotherapeutic agents usually induce systemic toxicity, drug resistance, and experience low cellular infiltration. Chemotherapy leads to the death of cancer cells along with normal cells instigating serious side effects. Considering these hindrances, CNTs can protect the chemotherapeutics, and in turn, lower their toxicity toward normal tissues by localizing the drug at the target site [78,79]. Their interaction with lipid membranes and intracellular transport mechanism is inadequately understood, but few studies have suggested that CNTs enter cells via various endocytic processes [80,81]. During tumor progression, increased tumor vascular permeability and insufficient lymphatic drainage lead to enhanced permeability and retention (EPR effect), which allows these nanoparticles to deliver the anticancer drugs to tumor sites rather than exposing healthy cells to these, thereby reducing toxicity [82]. Table 3 provides a list of various carbon nanovectors explored in the treatment of cancer.

Many anticancer drugs have been successfully conjugated with CNTs, such as doxorubicin, flutamide, cisplatin, methotrexate, paclitaxel, etc. Chu et al. prepared integrin-binding arginine-glycine-aspartic acid (iRGD)-conjugated polyethyleneimine (PEI) functionalized MWCNT conjugated with candesartan (CD). They assembled the formulation with plasmid AT (2) (pAT(2)). They targeted avb3-integrin and AT1R of tumor endothelium and lung cancer cells with iRGD-MWCNT-CD. The anticancer drug molecule displayed synergistic downregulation of vascular endothelial growth factor VEGF upon uniting with pAT (2) and inhabited angiogenesis effectually [83]. Karimi and others fabricated multiwalled CNTs conjugated with folic acid through ethylenediamine coupling. They reported that high cancer cell death was achieved via thermal ablation induced by the CNTs. You and co-workers demonstrated the effective anticancer agent delivery to brain glioma as evident by in vitro and in vivo studies. In vitro studies were performed on rat glioma cells (C6) and human glioma cells (U87 and U251), whereas in vivo studies were conducted on mice with induced orthopedic brain glioma. From the cytotoxicity studies, they reported that the prepared complex is more cytotoxic than free oxaliplatin and suggested that functionalized MWCNTs can be a good carrier for orthotopic brain tumors. [78].

Various herbal anticancer compounds such as curcumin [84,85], paclitaxel [86], docetaxel [87], vinca alkaloids [88], camptothecin [89], quercetin [90], oridonin [91], etc., have

been effectively combined with CNTs for their delivery to cancer cells. Zhao et al. also developed a multi-stimuli responsive drug delivery system for combinational chemotherapy and photothermal therapy. They fabricated mesoporous carbon nanoparticles (MCN) that displayed high loading efficiency of DOX and used them as near infrared-responsive drug carriers. Human serum albumin (HSA) was attached to the pore openings of MCN via disulfide bonds and was used as a concierge owing to its biocompatibility and apposite molecular size. The dispersity and biocompatibility of the developed system were enhanced by PEG functionalization. The drug release was pH-responsive, and in vitro studies showed laser power and concentration-dependent photothermal conversion capacity. Biodistribution studies exhibited prolonged retardation of DOX at tumor sites. In vivo antitumor studies revealed that MCN/DOX with NIR irradiation displayed the highest tumor inhibition rate against 4T1 tumors in mice. They concluded that the fabricated MCN/DOX system could be discovered as a multi-responsive drug release platform for combinable photothermochemotherapy [92]. Mehra and Jain prepared DOX-loaded folic acid and estrone-anchored PEG functionalized MWCNTs for the targeted release of drug. They reported the expanded survival period of the experimental model in comparison to the animals treated with free drugs [93].

2.4. CNTs for Vaccine Delivery

A vaccine must instigate a potent immune response at the cellular or humoral level. At the cellular level, it excites cytotoxic T cells, which mark and abolish infected cells, whereas, at the humoral level, vaccines rouse the making of counteracting antibodies which helps opsonization and following pathogen removal. For diseases such as HIV or malaria, vaccines need both cellular and humoral responses for the deterrence of infection and the abolition of circulating pathogens [94]. The immune system (innate and adaptive) comprises a collection of cells that circulates within the body as well as resides at the site of entry points such as skin, respiratory, gastrointestinal, and genital tracts, waiting to counter invading pathogens. The innate immune cells such as macrophages and neutrophils identify pathogens instantly and abolish them through the activation of different antibacterial effector functions. T and B cells are crucial for the instigation of the cell-mediated and humoral immune system. T cells with $CD4^+$ helper T cells stash various cytokines to control the functions of B cells, whereas $CD8^+$ T cells identify and terminate virus-infected cells [95].

Vaccine delivery faces many issues such as inappropriate absorption, the probability of antigen-caused hypersensitivity, anaphylactic responses, and adjuvant vaccine aversion. A lot of new tactics have been tested to boost vaccine delivery and owing to the adjuvant action, CNTs have also been implied for vaccine delivery to improve the action of the vaccine. The structure of SWCNTs is 100% surface atoms and thus, they allow the conjugation of various antigens onto their surface. The delivery of vaccines/antigens can be promoted by the engulfment of the system by phagocytic cells, inducing an immune response [96].

Various types of immune cells such as macrophages, monocytes, natural killer cells (NK), dendritic cells, T and B cells are known to uptake CNTs [97]. At the same time, CNTs did not hamper the health of these cells, due to their non-toxic nature [98]. It is imperative to modify the surface of the single or multiwalled CNTs for the induction of diverse reactive moieties which later can be utilized for the addition of antigenic peptides and proteins as well as vaccines. Chemical modification of the CNTs renders a high dispersion of vaccines, thereby enhancing the performance of the antigen in terms of their pharmacokinetic and pharmacodynamic behavior [5]. Yang and co-workers demonstrated that MWCNTs and tumor lysate protein (tumor cell vaccine) conjugate specifically enhanced the efficacy of antitumor immunotherapy in a mouse model bearing the H22 liver tumor [99].

The characteristic feature of CNTs to link various antigens or immune stimulants, which enables them to be attached to bacterial, viral, and protozoal antigens. Pescatori et al. demonstrated a microarray profiling of THP-1 (a monocytic cell line) with both functionalized and non-functionalized CNTs, which activated several *genes* involved in monocyte response to infection or vaccination such as nuclear factor kappa-light-chain-enhancer of

activated B cells (NF-κB), interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), along with others [97].

2.5. CNTs for Gene Delivery

The introduction of nucleic acids has created great curiosity in disease treatment to regulate, repair, restore, add, and/or seize a specific genetic site essential for disease indication. *Gene* therapy may well be utilized for the delivery of nucleic acids either through viral or non-viral vectors. Viral vectors have shown raised efficacies in transfection, but their clinical application is stalled by the glitches of immunogenicity and oncogenicity, lack of cell targeting potential, and low genetic payload [100]. Non-viral vectors possess an upper hand over viral vectors, as they are safe, can deliver *genes*, and they are reasonably inexpensive. Several non-viral vectors (*gene* carriers) including nanoparticles, peptides, dendrimers, liposomes, carbon nanotubes, etc. have been investigated for *gene* delivery [101]. CNTs have been widely utilized for the delivery of nucleic acids. The chemical modification of pristine CNTs (single or multi-walled CNTs) for example, aminated or carboxylated or strengthened CNTs using the proton-rich polymer polyethyleneimine (PEI) offers them litheness for *gene* therapy. SWNTs or MWNTs offer benefits of effectual surface modification for the designing of nanovectors for effective *gene* therapy. Varkouhi and his group investigated two cationically functionalized (CNT-PEI and CNT-pyridinium) CNTs for siRNA delivery. They reported that both functionalized CNT-complexed siRNAs showed 10–30% silencing activity and reduced cytotoxicity against H1299 cells. They stated that the type of functionalization of CNTs resulted in a non-cytotoxic CNT-based delivery system [102]. Tan et al. non-covalently functionalized SWCNTs with PL-PEG-NH or PL-PEG-maleimide. They further conjugated the functionalized SWCNTs with a 5′-thiolated siRNA against GFP (siGFP) and RFP (siRFP). They evaluated the silencing of GFP and RFP expression by SWCNT–siRNA via fluorescence spectroscopy and reported a 50–80% GFP expression knockdown in H1299, HeLa, MCF-7, and 293T cells by SWCNT-siGFP. They also observed *gene* silencing despite incubation with inhibitors on different cellular internalization pathways. The SWCNT–siRNA showed successful knockdown of GFP expression in different cell lines, indicating the release of siRNA into the cytoplasm, which silenced the *gene* expression.

Table 3. Various carbon nanovectors used in the treatment of tumors.

S. No.	Carbon-Based Nanovectors	In Vitro	Indication	Reference
1.	Hyaluronic acid-modified carbon dots	4T1 cells	In vivo anti-tumor activity	[103]
2.	Poly(ethylene glycol)-block-poly(β-benzyl-L-aspartate) (PEG-b-PBLA) polymers, octadecyl amine-p(Asp-API)10 (OAPI) polymers, and legumain-cleavable linker containing doxorubicin (DOX)-carbon quantum dots conjugations (CDs-C9-AANL-DOX)	Tumor cells	In vivo anti-tumor activity	[104]
3.	Tegafur loaded graphene oxide nanosheet	Molecular dynamics simulation survey for drug release across the cell membrane	Antitumor activity	[105]
4.	Epirubicin loaded multi-walled CNTS	T24 and 5637 cells	Bladder cancer	[42]
5.	Single-walled CNTs	4T1 cells	Chemo-photothermal therapy	[106]
6.	Single-walled CNTs	Human breast cancer cell (MCF-7)	-	[107]
7.	Single-walled CNTs	A549 and NIH 3T3 cells	-	[84]
8.	Multi-walled CNTs	HeLa cells	Photothermal therapy	[108]
9.	Double network structured GO	HCT116 cells	Chemo-photothermal	[109]
10.	Graphene QDs	BT-474, MCF-7 cells	-	[110]
11.	Graphene QDs	PANC-1, A-549, HepG2	-	[111]
12.	PEG functionalized multi-walled CNTS	U87, U373MG, NHA	Brain tumor therapy	[112]
13.	Multi-walled CNTs	MCF-7 and MDA-MB-231 human breast cancer cells/rats	-	[113]

3. Graphene/Graphene Oxide/Reduced Graphene Oxide

Graphene and its derivatives are the material of thoughtful consideration because of its inimitable inherent assets such as highly interesting photoluminescence properties as well as easy surface functionalization, which leads to its applicability in various biological settings [114]. The large surface area, chemical purity, and free π-electrons lend graphene a suitable candidate for the delivery of therapeutics [115], whereby conjugation strategies can

enhance the biocompatibility and residence time in vivo [116]. These materials have been explored for the delivery of chemotherapeutic agents [117], *genes* [118], peptides [119], and tissue engineering [120]. Hummers (1958) developed graphene oxide by the vigorous oxidation of graphite [121]. A schematic illustration of their use is given in Figure 6. Graphene oxide possesses unique structural features such as large and planar sp^2 hybridization of carbon, high surface area, and augmented oxygen-containing groups. Oxygen groups offer biocompatibility, physiological solubility, and stability to GO, and the high payload of drugs/*genes* via chemical conjugation or physisorption tactics can be achieved. Graphene oxide used for drug delivery is generally one to three layers thick with a size ranging from a few nanometers to several hundred nanometers [122].

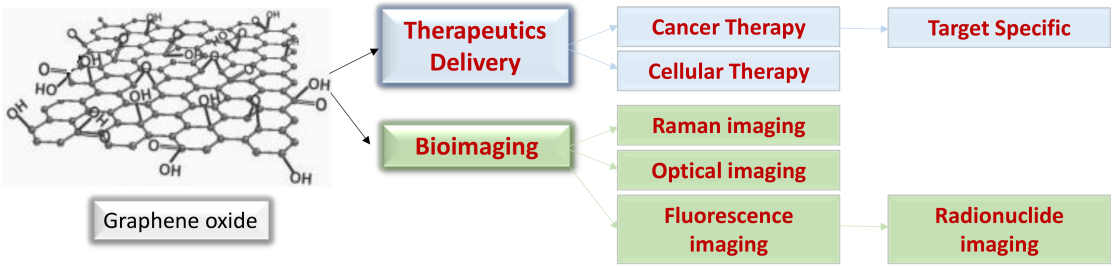

Figure 6. Various applications of graphene oxide in the biomedical arena. Adapted from [123].

3.1. Techniques for the Fabrication of Graphene

Graphene can be synthesized using two methods: i.e., bottom-up and top-down synthesis methods. The synthesis methods lend excellent properties to these materials. The interaction between therapeutics and graphene-based materials depends on their properties such as layer number, lateral dimension, chemical residual, surface charge, and surface functional groups.

Bottom-Up Synthesis: This method includes three procedures: (i) epitaxial growth on silicon carbide; (ii) the chemical vapor deposition method (CVD); and (iii) the plasma-enhanced chemical vapor deposition (PECVD) method. The first method [124] uses the thermal decomposition of silicon carbide at high temperatures under vacuum or in inert gas. As carbon has negligible vapor pressure in comparison to silicon, graphene layers are formed on the silicon carbide surface after silicon sublimation. Large surface area graphene can be produced by the CVD method. In this method, a precursor gas (e.g., methane, acetylene, ethylene, propene) containing hydrocarbon molecules are charged into the reactor, in which the hydrocarbon molecules are catalytically decomposed into carbon radicals and arranged into graphene structures on the catalytic layer of the substrate (Ni, Cu, Rh, Co, or alloys). The properties of the fabricated graphene such as layer number, crystal size, and layer number are largely affected by several factors such as precursors, assistant gases, catalyst layer, and temperature. PECVD shows an advantage over CVD in the synthesis of graphene at a relatively low temperature with reduced deposition time. It also resolves the evaporation problem of a catalyst layer at high temperatures.

Top-Down Synthesis: This method helps in the segregation of graphene sheets from high-quality graphite, which contains stacked multi-layer graphene using a mechanical or chemical method. It involves mechanical and chemical exfoliation methods and the GO reduction method. The mechanical exfoliation method is used to separate graphene from graphite using a scotch adhesive tape to break the van der Waals force between the layers of graphite by a repeated sticking and lifting process [9], producing high-quality graphene, but it lacks large-scale production ability. On a large scale, graphene can be fabricated using the reduction of graphene (rGO) method. This method involves GO production and GO reduction to rGO by the method described by Hummers [121]. The oxidation process involves the reaction of graphite with sodium nitrate, concentrated sulfuric acid, and potassium permanganate, which introduces oxygen-containing functional groups onto graphite sheets. The graphene oxide layer can be separated by ultrasonication in a polar

solvent, e.g., water because of the introduction of enlarged layer space due to the insertion of functional groups.

3.2. Functionalization of Graphene

For their biomedical use, graphene-based materials should be functionalized for the same reasons mentioned above for CNTs. This can be achieved for instance via PEGylation [125] or coating with dextran [126], both of which decrease their toxicity and augment their biocompatibility. Surface functionalization can be achieved by non-covalent and covalent binding.

Non-Covalent Functionalization: This method involves forces such as hydrophobic interactions, π–π stacking, or electrostatic binding between the graphene-based materials and the active molecules. The hydrophobic interactions are utilized to absorb the aliphatic parts of surfactants onto the graphene by the interaction of polar parts of surfactants [127], thus enhancing the stability of surfactant-functionalized graphene or rGO in polar solvents. Electrostatic interactions can also be used for the functionalization of these materials, since GO sheets are negatively charged, and consequently, a positively charged biomolecule can be electrostatically adsorbed to the surface of the GO surface [128,129]. The same strategy can also be used to flexibly modify the GO surface with polymers and targeting ligands [130].

Covalent functionalization: The functional groups such as the carboxyl, epoxy, and hydroxyl groups on the GO can be used for covalent functionalization. Similarly, the carboxylic acid group of GO can be utilized for the amidation reaction with the amine group in polymers [131]. PEI functionalization was achieved on poly(acrylic acid) modified GO upon the reaction of ethyl(dimethylaminopropyl) carbodiimide/N-hydroxy succinimide EDC/NHS with the carboxylic acid group. This covalent functionalization augmented the in vitro proliferation and focal adhesions in hMSCs of the GO–PEI nanocomposites [132]. Due to its highly cationic charge density, PEI can also be electrostatically adsorbed to the GO surface (as outlined above) and thus serve as a versatile platform for further functionalization based on amine chemistry [130].

3.3. Graphene Oxide for Drug Delivery

Several hydrophobic drugs, for example, doxorubicin and docetaxel, can be adsorbed onto graphene using simple physisorption via π–π stacking, along with antibodies for the selective targeting to cancer cells. π–π stacking and electrostatic or hydrophobic interactions of graphene provide a high carrying capacity of poorly soluble drugs deprived of conceding drug strength. Table 4 summarizes the application of GO-based drug delivery.

Boran et al. conjugated graphene oxide with zoledronic acid (ZOL-GO) and evaluated these in vitro on cells. They explored the allied morphological changes of bone marrow-derived mesenchymal stem cells (BM-MSC) and MCF-7 breast cancer cells along with the effect of the drug on the mineralization of BM-MSCs. They reported that the nanostructured ZOL-GO facilitated the mineralization of BM-MSC cells, which was demonstrated by the formation of clusters around the cells. The Boran group concluded that the ZOL-GO nanostructures can be a promising drug complex for the treatment of osteoporosis and metastasis [133].

Islami et al. constructed efficient quercetin-loaded single-layer graphene oxide (GO) sheets grafted with hyperbranched polyglycerol (HPG) on the surface of GO through the ring-opening hyperbranched polymerization of glycidol. The fabrication was carried out using both a modified and improved Hummers method. HPG improved the stability of GO sheets in biological fluids with augmented drug-loading capacity and high encapsulation efficiency. HPG-GO displayed the controlled and sustained release of quercetin and suggested that an acidic pH could aid in the drug release. Moreover, the HPG-GO did not exhibit cytotoxicity on the MCF-7 cell line in diverse concentrations during 72 h incubation [134].

Yang et al. developed a magnetic and bio dual targeting GO–Fe nanoparticle hybrid. From the in vitro experiments, they demonstrated that the drug delivery cargo not only enhanced the anticancer outcome but can also provide site-specific targeting of the SK3

human breast cancer cells by the magnetic field guided GO–Fe nanoparticles. Yu et al. designed an α, β6-targeting peptide (HK-peptide) functionalized and photosensitizer (HPPH)-coated graphene oxide (GO (HPPH)-PEG-HK), which triggered the dendritic cells and expressively barred the tumor growth and lung metastasis by increasing the intrusion of cytotoxic $CD8^+$ T lymphocytes in the interiors of the tumors as evinced by in vivo optical and single-photon emission computed tomography [135].

The Cheon group fabricated a doxorubicin-loaded BSA functionalized graphene sheet for combinational chemo- and photothermal therapy in brain tumors [136]. Fong et al. developed hyaluronic acid-chitosan-g-poly (N-isopropyl acrylamide) grafted DOX-folic acid-GO thermosensitive hydrogel for breast cancer therapy [137]. Shao et al. fabricated a mesoporous silica-nanoparticles coated with polydopamine functionalized with rGO, followed by modification with hyaluronic acid and loaded with DOX. The developed system was pH-dependent, which triggered the release of the chemotherapeutic agent and proved to be an effective carrier for cancer therapy [138].

3.4. Graphene Oxide for Gene Delivery

Graphene-mediated *gene* delivery has emerged as a novel technique where graphene derivatives have shown tremendous potential for *gene* transfection. However, it is essential to modify graphene derivatives with polymers to render them with cationic surface properties, which facilitate electrostatic interactions with anionic oligonucleotides. To date, PEI and poly(sodium 4-styrenesulfonates) have been well thought out for *gene* delivery via graphene derivatives [139–141].

Zhang et al. observed the use of PEI-conjugated GO to deliver DOX and siRNA. They demonstrated that the conjugate not only enhanced the therapeutic efficiency but also led to an increment in safety [142]. Similarly, Feng et al. explored the effects of PEI (1.2 kDa and 10 kDa) on the cytotoxicity of PEI-GO [129]. Cao and the group reported the role of lactosylated chitosan oligosaccharide LCO-functionalized GO in the removal of toxicity and the enhancement of loading efficiency of fluorescein amidites (FAM)-DNA to human hepatic carcinoma cells (QGY-7703) [143]. Liu and his group fabricated a graphene-based *gene* vector by employing graphene-oleate-polyamidoamine (PAMAM) dendrimer hybrids owing to the high dispersion and stability of graphene in water solutions. The hybrid was developed by using oleic acid and covalent binding of PAMAM dendrimers. The group investigated the plasmid DNA transfection capacity and its cytotoxicity toward HeLa and MG-63 cells. They reported that the developed hybrid was biocompatible to HeLa cells, and the cell viability retains about 80%, although the hybrid was cytotoxic to MG-63 cells at concentrations above 20 mg/mL [144].

Table 4. Application of graphene derivatives for drug delivery.

S. No.	Graphene Derivative	Therapeutic Agents	Application and Outcomes	References
1.	GO	Zoledronic acid	Bone marrow-derived mesenchymal stem cells (BM-MSC), and Michigan Cancer Foundation-7 (MCF-7) breast cancer cells	[133]
2.	Pristine graphene and graphene oxide	Doxorubicin	In vitro: pH simulation	[145]
3.	Graphene oxide	Doxorubicin	In vitro: drug release	[146]
4.	GO-FA-AuNPs	Doxorubicin	Significant in vivo tumor reversion in solid tumor model in Balb/c mice	[147]
5.	GO nanosheets doped into ZnO NPs	Doxorubicin	GO-doped ZnO NPs displayed higher drug loading efficiency of 89% in comparison to 82% of ZnO. The developed system enhanced the dissolution of the drug.	[148]
6.	PEG-functionalized GO	Cephalexin	In vitro, CEF release exhibited burst release followed by sustained release over the 96-h period with a cumulative release of 80%. MIC values stated dose and time-dependent antibacterial activity for GO-PEG-CEF against both Gram positive and Gram negative bacteria.	[149]
7.	GO-PVP	Quercetin and gefitinib	Dual drug loaded GO-PVP nano-vehicles showed higher drug loading, and cancer cell cytotoxicity was more in contrast to an individual GO-PVP system in PA-1 ovarian cancer cells and compared to their effects on IOSE-364 ovarian epithelial cells.	[150]
8.	GO	Ampicillin, chloramphenicol and tetracycline	GO potential as an antibacterial along with antibiotic drugs displayed synergistic effects against *S. aureus*, *E. coli*, *E. faecalis*, and *P. aeruginosa* and the toxicological effects of GO toward human epidermal keratinocytes (HaCaT).	[151]
9.	PEGylated GO	Doxorubicin	PEGylation of the GO efficiently augmented the average water density around the nanocarrier, which acts as a barricade, leading to the DOX migration to the solvated PEG-free part of the GO surface. The computational results exhibited the fact that increasing the PEG chain length aids DOX loading on the nanocarrier.	[152]

4. Graphene Quantum Dots (GQDs)

Graphene quantum dots (GQDs) have found their place recently as the newest member of the carbon nanomaterial family. GQDs comprise a few layers of graphene, and its functional group has a lattice distance of about 0.24 nm with sp^2 hybridization, which is somewhat similar to a small flake of graphene. They can be differentiated from carbon quantum dots (CQDs), which possess a lattice distance of about 0.34 nm, and further, CQDs are amorphous with sp^3 hybridization. GQDs possess characteristic photoluminescence owing to quantum confinement. Also, GQDs hold the same features as graphenes such as large surface area and free π-electrons availability, which lends them suitable for imaging, sensing, cancer therapy, etc. [153–155].

GQDs for Drug Delivery

The oxygen-rich surface of the GQDs is the key feature that makes them suitable for drug adsorption and enhancing colloidal stability in vivo, along with the features of a single atomic layer and small size. The fluorescent characteristics of graphene quantum dots render them traceable when targeted to e.g., cancer cells [156]. Tian et al. developed a framework of zeolite imidazolate (ZIF-8)-embedded DOX-loaded GQDs, which showed an acidic pH-responsive drug release behavior [157]. Zheng et al. demonstrated intracellular drug delivery and real-time drug release from DOX-loaded aptamer/GQD-capped fluorescent mesoporous silica nanoparticles. Under the extracellular conditions, the fluorescence of the fluorescent mesoporous silica nanoparticles (MSNs) remains off at a low ATP level. When the nanocarrier is recognized and internalized into the target tumor cells by an AS1411 aptamer, in the ATP-rich cytoplasm, the ATP aptamer causes the shedding of the GQDs from the nanocarriers, thus resulting in drug release and at the same time, the fluorescence of MSNs provides real-time imaging possibility [158].

The Wei group developed DOX-loaded GQDs and conjugated them with Cy5.5 dye via a cathepsin D-responsive (P) peptide, which augmented tissue penetration and cellular uptake of the drug. The cell uptake in 4T1 cells and the drug release was monitored by confocal laser scanning microscopy. The GQDs-treated cells displayed blue fluorescence, exhibiting the internalization of the developed formulation. They reported superior therapeutic performance both in vitro and in vivo due to the enhanced tissue penetration and cellular uptake. The developed system served as probes for programmed tracking of the drug delivery and release process, as well as drug-induced cancer cell apoptosis via the GQDs, doxorubicin, and Cys fluorescence. The Nigam group fabricated a GQD-conjugated gemcitabine-loaded HAS nanoformulation for the targeted delivery of the drug to the tumor cells with the help of albumin via the gp60 pathway [159].

5. Fullerenes

Buckyball clusters or buckyballs, also known as endohedral fullerenes, include fullerenes, buckminsterfullerene, and C60, which are composed of fewer than 300 carbon atoms. Fullerenes possess numerous functional points that permit the attachment of chemical groups of targeting ligands in three-dimensional orientations, which could facilitate cellular targeting. It is also possible to modify their allotropes to optimize pharmacokinetic characteristics, therapeutic effects, and other attributes such as size, hydrophilicity, and colloidal stability in a biological environment.

5.1. Techniques for the Fabrication of Fullerenes

Fullerenes can be synthesized via the pyrolysis of polycyclic aromatic hydrocarbon as naphthalene, corannulene, or higher polycyclic compounds. These compounds are decomposed at high temperatures (around 1000 °C) with the cleavage of hydrogen bonds and production of mainly C60 and C70, in the presence of an inert gas (argon). Fullerenes can also be fabricated by an arc-discharge method between two graphite electrodes by applying high voltage. The discharge induces vaporization of the graphite with the formation of plasma. Fullerenes are synthesized by condensation of the graphite plasma in particles that get deposited onto the reactor walls [160].

5.2. Functionalization of Fullerenes

Fullerenes are functionalized to overcome the problems of poor water solubility and low solubility in several organic solvents [161]. Their surface can be functionalized by the use of solubilizing agent complexation to partially mask the surface of the fullerenes and by covalent functionalization [162]. The presence of double bonds in the fullerene structure lends them to be modified greatly by functional groups of choice [163,164]. Fullerenes are comprised of carbon of erratic size and molecules that look like a hollow sphere or tube. They are composed exclusively of carbon in varying sizes resembling a hollow sphere, ellipsoid, or tube [6] with a strong apolar character that enables them to develop into lipid-like systems that can easily cross biological membranes [165].

5.3. Fullerenes for Drug Delivery

Zhao's group prepared a fullerene-based (C82) DOX-loaded, cyclic RGD (DOX-C82-cRGD) complex for lung cancer treatment that possessed probable clinical effectiveness [166]. Hazrati and co-workers constructed a $C_{30}B_{15}N_{15}$ heterofullerene carrier system by employing the density functional theory for the delivery of isoniazid. They reported that the interaction of the -NH_2 group of isoniazid with the boron atom of the fullerene engendered a high amount of energy, which altered the fluorescence emanation of the $C_{30}B_{15}N_{15}$ that caused the parting of isoniazid from the surface of the carrier by proton attack at a low pH of cancerous tissues [167].

Tan and co-workers fabricated a biocompatible and water-soluble fluorescent fullerene (C60-TEG-COOH)-coated mesoporous silica nanoparticle, which delivered the DOX in a pH-responsive manner, and the cellular uptake of nanoparticles was detected via the green fluorescent property of the C60 [168]. Fullerenes have also found their application in the delivery of anti-inflammatory agents. Recently, C60 fullerenes have been recognized to persuade the suppression of Ag-driven type-I hypersensitivity through the prominent prevention of an IgE-dependent mediator. Hence, they can manage the mixt mast-cell-dependent allergic inflammations, asthma, inflammatory arthritis, heart diseases, and multiple sclerosis [169]. Also, fullerenes exhibit anti-inflammatory properties by stabilizing mast cells and peripheral blood basophils and inhibiting the release of proinflammatory mediators [170].

5.4. Fullerenes for Antibody/Antiviral Delivery

Fullerenes due to their excellent surface structural properties have also been utilized in the delivery of antibodies. Ashcroft and co-workers successfully conjugated antibodies to fullerenes by using a novel water-soluble C60 derivative as the fullerene scaffold. The scaffold was modified through the Bingel–Hirshc reaction and an antibody ZME-018 was covalently attached through the disulfide bridge exchange. ZME-018 explicitly targets the gp240 antigen present in over 80% of the human melanoma cells [171]. Fullerenes were also functionalized to produce a photoactive stage for the distant deactivation of viruses and bacteria. Kim and his group fabricated a substratum of hot-pressed silica particles placed on a metallic substrate functionalized with 3-aminopropyltrietoxysilane and amine groups to covalently couple the fullerenes. The research group studied the inactivation of the MS2 bacteriophage at predefined distances from the irradiated surface and reported disinfection of the bacteria and virus by the immobilized C_{60} in the gas phase via photosensitization, contrary to singlet oxygen ($^1O_2$), which was effective up to around 10–15 cm from the surface [172].

6. Nanodiamonds

Nanodiamonds (NDs) are the newest exposed allotropes of carbon with a large surface area and a single crystal size of 2–8 nm. NDs are mostly created by the detonation process [173] and chemical vapor deposition methods [174]. They are nanocrystals with tetrahedral carbon atoms in a 3D cubic trellis owning a diamond-shaped structure with electrical properties of diamond, coated with an onion-like graphite shell. Their surface comprises functional groups formed on the ND surface after purification stemming from

the residual (non-diamond) carbon as a result of the detonation process, usually containing oxygen, such as hydroxyl, carboxylic acid, ketone, lactone, and ether. NDs with nitrogen vacancies in their center, thus exhibiting photoluminescence characteristics are termed fluorescent NDs (FNDs) and have found highly interesting applications in bioimaging [175–177].

The ND physicochemical properties such as size and surface chemistry are highly decisive for their fluorescence properties [178]. NDs are very seldom present as single crystals in solution, the aggregates of which determine their size during application. Nevertheless, these aggregates are often hydrophilic due to the functional groups and can thus still form a stable aqueous colloidal suspension [179,180], which is imperative for their biomedical applicability. Due to this property, NDs have also been proposed as drug carriers, whereby the large surface area is exploited for adsorbing or linking numerous drug moieties on the surface of the NDs by covalent and non-covalent functionalization methods [181]. However, given the diversity of the ND surface owing to the production method, the precise surface chemistry of ND is challenging to control and define. Another widely employed strategy to make use of the intrinsic photoluminescent properties of ND while increasing their drug-carrying capacity is by coating the ND with shells of other materials that can harbor drug molecules in much higher amounts than what can be adsorbed onto the native ND surface or otherwise improve their biomedical applicability [182–184]. The drug adsorption onto native nanodiamonds depends on parameters such as maximal monolayer capacity, binding strength, and the degree of drug removal from the solution. The various applications and advantages of NDs are illustrated in Figure 7.

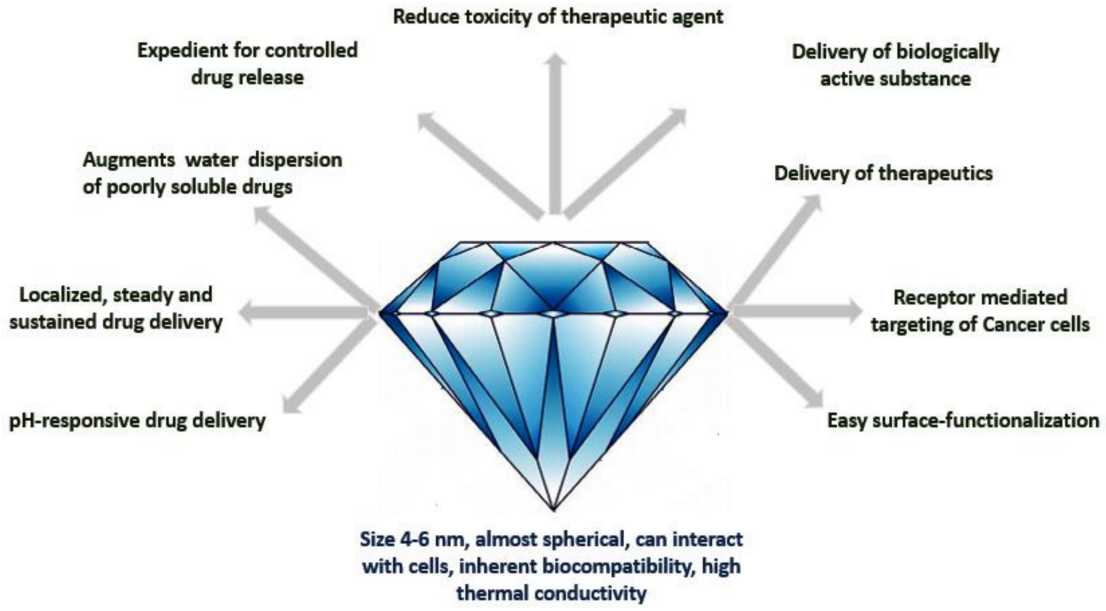

Figure 7. Applications and advantages of nanodiamonds. Adapted from [28].

Nanodiamonds for the Delivery of Therapeutics

The Li group successfully treated the immunosuppression associated with glioblastoma with DOX–polyglycerol–ND composites. They developed cellular and animal GBM models by THP-1 derived dendritic cell and female athymic Balb/c nude mice correspondingly. The group reported that the nanocomposite could rouse the immunogenicity of glioblastoma cells both in vivo and in vitro, by persuading autophagy and emanating antigens from the glioblastoma cells [15]. Roy et al. formulated -COOH functionalized and -NH_2 functionalized NDs loaded via monolayer surface adsorption with efavirenz. They revealed that the bioavailability of the efavirenz was augmented, and non-functionalized NDs possessed higher drug-loading capacity than the functionalized NDs. They demonstrated that the functionalized NDs can infiltrate the blood-brain barrier and release the drug in the central

nervous system using an in vitro BBB model of primary human brain microvascular endothelial cells and astrocytes. Neural stem cells can multiply and segregate into astrocytes, neurons, and oligodendrocytes. This differentiation of neural cells can be helpful in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's [185].

Nanodiamonds can boost neural stem cell adhesion and differentiation. In a trial, Taylor et al. demonstrated that the NDs supports rodent neuronal outgrowth. They inspected the interaction of human neural stem cells with the NDs [186]. Edgington and Jackman nurtured human neural stem cells with oxygen and hydrogen functionalized monolayers of NDs and evaluated neural stem cell adhesion and proliferation for seven days and stated that the adhesion and proliferation were higher with oxygen functionalized NDs than the hydrogen functionalized NDs. It was reported that the NDs monolayers can provide comparable physicochemical characteristics of extracellular matrix protein. Their report suggested that the NDs can be a substratum for neuronal growth and be a possible applicant in neurodegenerative brain disorders [187].

7. Carbon Nano-Onions

Carbon nano-onions (CNOs) are zero-dimensional carbon nanoparticles that are categorized by their multi-layered closed shells all-encompassing one another, similar to that of an onion. These CNOs possess a diameter in the range of 1.4 to 50 nm with an interlayer distance of approximately 3.4 Å with a C60 or C80 fullerene at their core (Figure 8) [188]. Structural and dimensional variations are bound and vast depending on the method of preparation [189]. CNOs can be fabricated through various techniques, which results in the production of CNOs of various shapes and sizes. DC arc discharge [10], electron beam irradiation [190], underwater arc discharge [191], thermal annealing under high vacuum [192], thermal annealing under helium environment [193], catalyst-free synthesis through thermolysis under Ar or air environment [194], and thermal reduction are the methods that can be used for the production of CNOs with tunable sizes and shapes.

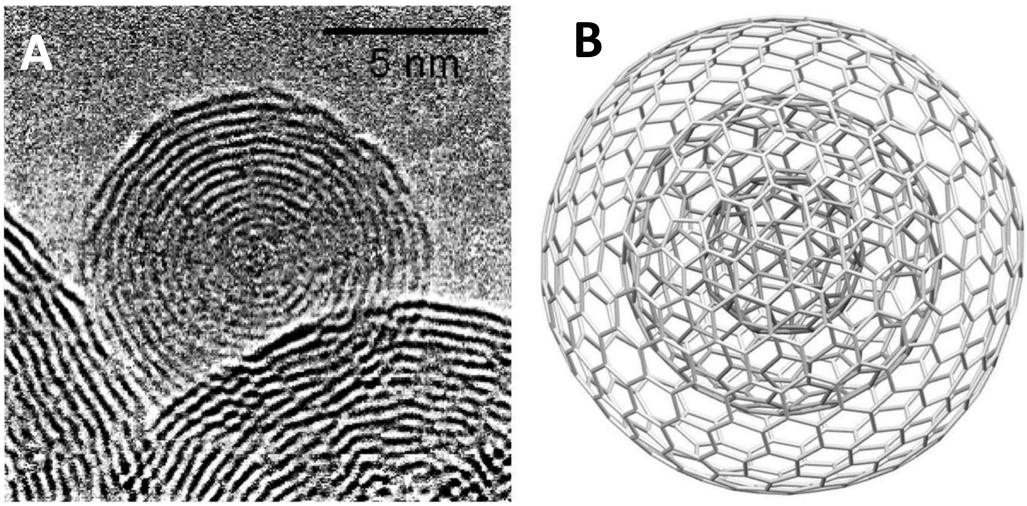

Figure 8. High-resolution TEM image of (**A**): Carbon onion; (**B**): Structure of carbon onion. Reproduced with permission from reference [195].

Pristine carbon nano-onions (p-CNOs) developed through the above-mentioned methods are hydrophobic, which leads to their aggregation in aqueous and organic solvents, even after sonication. Their solubility and dispersibility can be amended via covalent and non-covalent surface modification [196]. The covalent functionalization of CNOs particularly by oxidation renders them with augmented water dispersibility, extending the possibility of amidation and esterification reactions of the carbon nano-onions. CNOs can be functionalized by non-covalent interactions via electrostatic interactions, van der Waal forces, and π interactions.

Carbon Nano-Onions for Therapeutics Delivery

Utilizing the functionalization of the CNOs, their application in various biomedical sections such as drug delivery, tissue engineering, bioimaging, sensing, CNOs as a drug for cancer, and CNS-related disorders have been vastly explored (Figure 9, Table 5). The supramolecular functionalization of CNOs via stimuli-responsive biocompatible polymers enables them to be an effective targeted drug delivery system. Narsimha and co-workers engineered 4-hydroxyphenyl methacrylate-carbon nano-onions (PHPMA-CNOs = f-CNOs) embedded bovine serum albumin (BSA) nanocomposite fibers by Forcespinning® (FS) technology for stimuli-responsive delivery of DOX. The group reported a slow and prolonged DOX release over a 15-day study along with augmented thermal properties and in vitro degradation. They tested the cytotoxicity of hydrogels with osteoblast cells that displayed good cell viability and cell growth. The developed system exhibited a pH-responsive sustained drug release over 15 days, which suggested that zein/f-CNOs hydrogel could be a potential drug delivery system for the colon [197].

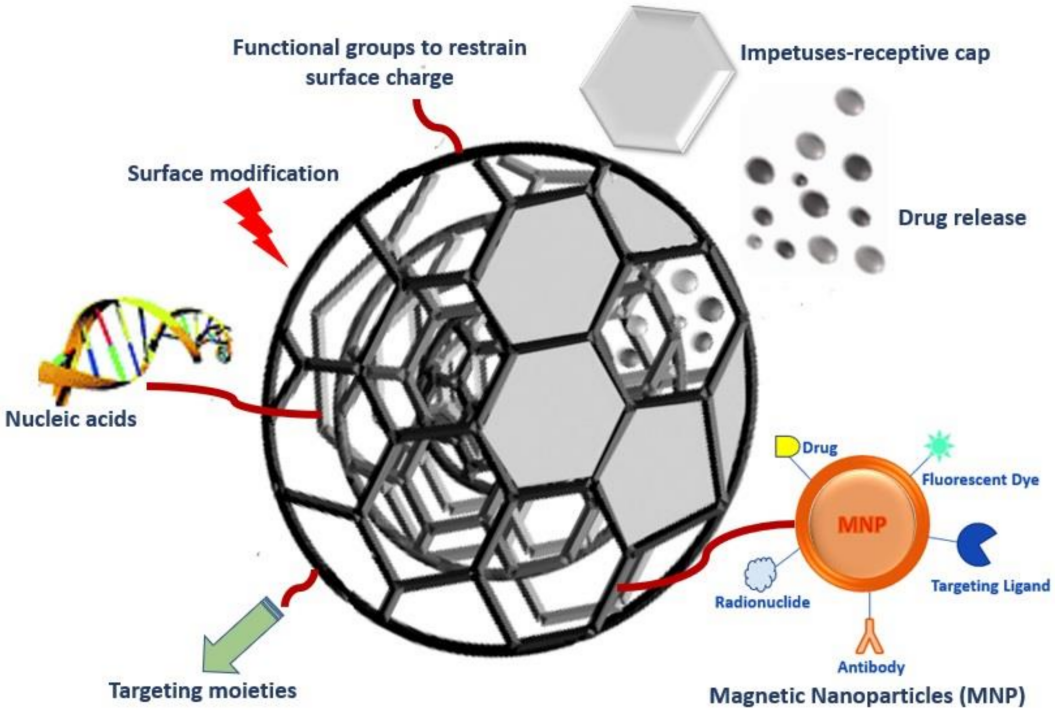

Figure 9. Graphic illustration of carbon nano-onions (CNOs) functionalization and applications. Adapted from [29].

D'Amora et al. functionalized CNOs non-covalently with hyaluronic acid-phospholipid (HA-DMPE) and successfully targeted CD44 overexpressed cancer cells. Functionalization augmented the solubility of the nanoconstruct, enhanced the in vitro cell toxicity in human breast carcinoma cells overexpressing CD44, and increased the uptake in comparison to human ovarian carcinoma cells with an imperceptible amount of CD44. They reported that the CNOs composite possessed high in vivo biocompatibility in zebrafish (*Danio rerio*) during the different stages of development and established CNOs localization in the digestive tract of the zebrafish larvae [198].

Carbon nano-onion/surfactant (CNO/surfactant) composites facilitate the manufacturing of soluble nanostructures by utilizing the hydrophilic attribute of surfactants and robustness of carbon structures in the fabrication of CNO/surfactant composites with enhanced solubility and other physicochemical properties. Bobrowska et al. employed hexadecyltrimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS), sodium dodecylbenzene sulfonate (SDBS), Triton X-100, and Tween 20 to functionalize the CNOs by the non-covalent technique. This method produced a stable, well-dispersed CNO/surfactant nanocomposite structure that was evaluated for its in vitro biological

activity against *E. coli*. Their study revealed that only the CNO/CTAB composite decreased the cell viability in vitro. They further reported that this activity could be allocated to the simple composite dissociation in water solutions, although antimicrobial assets of the composites are better to some extent in comparison to pure CTAB, indicating a synergistic effect of the CNO/surfactant nanocomposite when compared to pure surfactant [199].

Babar and co-workers reported an interaction between calf-thymus (CT) double-stranded DNA (dsDNA) and water-soluble carbon nano-onion (wsCNO) in water that followed denaturation of dsDNA (double-stranded DNA) to ssDNA (single-stranded DNA). The ssDNA concomitantly wrapped with the spiked surface of wsCNO and created a triangular aggregate confirmed by SEM images, which further aggregated to form a six-petal flowery arrangement hexagonally and reached a dead-end network as evident by SEM and optical fluorescence microscopy. This dead-end network aggregate lacked the intrinsic optical property of DNA and displayed a loss of its activity (Figure 10). The researchers finally concluded that the wsCNO being non-toxic can be explored to control the unwanted proliferation of rouged DNA by interacting with wsCNO, which can be utilized for the prevention of such viral DNA replication in recognized diseases [200].

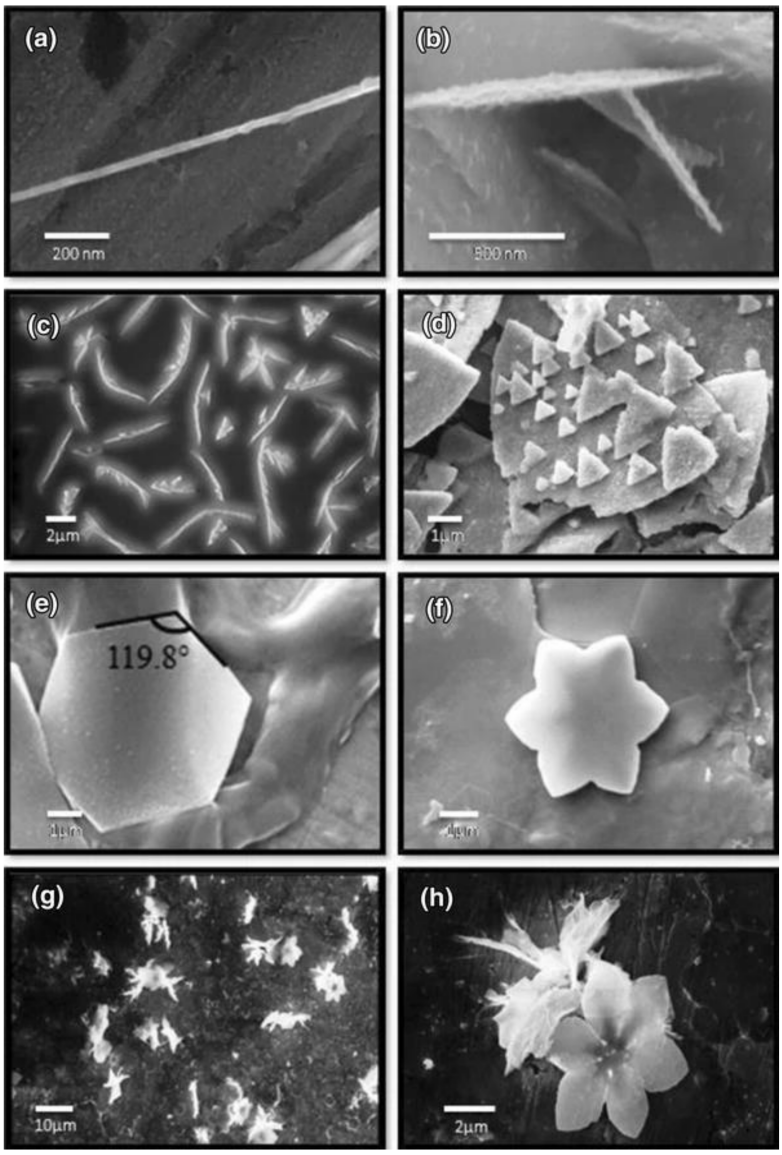

Figure 10. SEM photomicrographs of DNA composites (**a**): DNA-water-soluble carbon nano-onion (wsCNO) at 1 h; (**b**): Growth at 4 h; (**c**): Aggregation at 4 h; (**d**): Triangle formation at 16 h; (**e**): Hexagon formation; (**f**): Flower formation; (**g**): Assorted flower formation; (**h**): Selected six-petal flower [200].

Tripathi et al. developed graphitic photoluminescent water-soluble carbon nano-onions (wsCNO) from the traditional pyrolysis of vegetable ghee without employing any metal catalyst through a simple oxidative treatment using nitric acid. The fabricated wsCNO possessed tunable photoluminescence behavior from the visible-to-near infrared region. They further segregated small-sized wsCNO from the bulk via gel filtration acquired a highly fluorescent colored fraction, which they used for cell imaging of *E. coli* and *Pseudomonas putida* and the selective, immediate detection of glucose molecules based upon a simple fluorescence "turn-off"/"turn-on" technique [201]. Pakhira and co-researchers demonstrated the successful crossing of small-sized wsCNO through the blood-brain barrier in the murine model of Cerebral Autosomal-Dominant Arteriopathy with Subcortical infarcts and Leukoencephalopathy (CADASIL) as well as in Glioblastoma Multiforme (GBM)-induced mice. They reported that the drug was readily eliminated from the animal model after a few days, signifying the probable use of water-soluble carbon nano-onions as a drug carrier [202].

Table 5. Recent progress of CNOs in biomedical applications.

S. No.	Delivery System	Application	Results	Reference
1.	Polycaprolactone/f-CNO nanocomposite fiber	Anticancer drug delivery	DOX release from PCL/f-CNO nanocomposite fiber was pH-dependent. F-CNOs augmented the mechanical strength, hydrophobicity, and biocompatibility of the PCL nanofibers.	[203]
2.	f-CNO-reinforced zein hydrogels	Anticancer drug delivery	f-CNOs improved the mechanical strength of zein hydrogels. The delivery system exhibited good cytocompatibility against the osteoblast cell line. A pH-responsive sustained drug release over 15 days was observed.	[197]
3.	f-CNO/gelatin composite hydrogels	Anticancer drug delivery	5-FU/f-CNO/Gelatin hydrogels exhibited augmented tensile strength in comparison to pristine gelatin hydrogels. A sustained release of 5-FU for over 15 days was observed, which indicated possible prospects in cartilage tissue engineering and drug delivery.	[204]
4.	Ox-CNO-loaded chitosan polyvinyl alcohol (CS/PVA/oc-CNO) nanocomposite film	Tissue engineering application	Ox-CNO enhanced the stability of the CS/PVA/ox-CNO scaffold. The nanocomposite film displayed no allergic response or pus formation in Wistar rats after subdermal implantation of the scaffold. The CS/PVA/oc-CNO scaffold exhibited tissue regeneration capability.	[205]
5.	Pristine CNOs (p-CNOs), ox-CNOs, far-red fluorescent-CNOs	Cellular imaging application	Ox-CNOS and Fluo-CNOs exhibited excellent cytocompatibility against MCF-7 and HeLa cells. Far-red fluorescent images indicated the internalization of fluo-CNOs by the MCF-7 cells, conforming that fluo-CNOs can be utilized as a high-resolution cellular imaging agent as an alternative for organic dyes.	[206]
6.	DNA sensor composed of glassy carbon electrode (GCE)/pristine-CNO	Sensing biomolecular interaction	The GCE/CNO nanocomposite DNA sensor sensed the human papillomavirus oncogene DNA sequence via amperometric detection. Modification via electrochemical grafting of the GCE/CNO surface with two different diazonium salts (4-aminophenylacetic acid) PAA and (4-aminophenylmaleimide) PM yielded GCE/CNO/PAA and GCE/CNO/PM nanocomposite. Both surfaces supported the attachment of thiolated or biotinylated short recognition DNA sequences (DNA probes). The large surface area and the enhanced electron transfer properties of this analytical sensor helped in the sensing of biomolecular interactions.	[188]
7.	CNO-based catalytic biosensor	Nanobiocatalyst for biosensing application	CNO-based catalytic biosensor (CNO/enzyme) conjugate retained optimum pH and temperature, displayed stability over a longer duration at 37 °C. The CNO catalytic biosensor efficiently detected the immobilization of various enzymes such as alkaline phosphatase, horseradish peroxidase (HRP), and glucose oxidase (≈0.5 mg of enzyme per mg of CNOs).	[207]

8. Toxicity Concerns for Carbon-Based Nanomaterials

There have been a lot of concerns on the safety issues of the biomedical applications of CNMs. Many of the toxicity and long-term effect concerns are related to the persistence of CNMs in biological systems. A series of information on the pharmacokinetics, metabolism, long duration of CNMs in vivo, and toxicity is required. Several studies have been conducted reflecting the conflicting outcomes over the toxicity of CNMs, concerning their successful biomedical application [208–212]. It has been demonstrated that concentration, lateral dimension, surface properties, types, and presence of functional groups markedly affect their toxicity in the biological environment (Figure 11) [213,214].

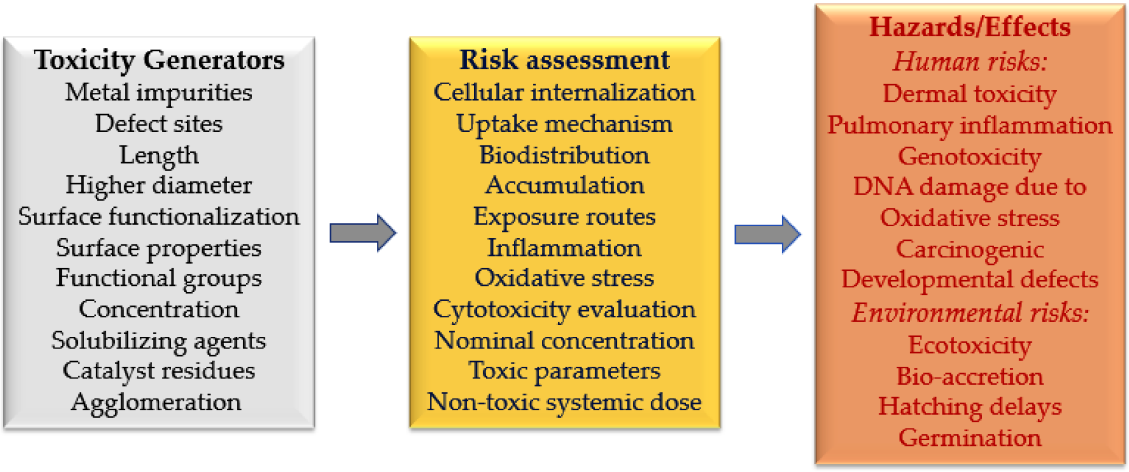

Figure 11. An insight on the factors causing toxicity, their risk assessment, and deleterious effects on humans as well as the environment by the carbon-based nanomaterials (CNMs).

The physical characteristics of CNTs such as fiber shape, length, and accumulation could affect the immunological responses and their accretion in tissues [215]. Shorter CNTs were reported to be less toxic than longer CNTs when injected subcutaneously. Shorter CNTs were found in the cytosol of the macrophage after 4 weeks, but longer CNTs were found to be free-floating and caused inflammation. This study confirmed that the toxicity of MWCNTs was length-dependent and was comparable with that of asbestos toxicity.

Wang et al. exhibited a cell mapping curve for various cells under similar conditions and stated that the GQDs having a size below 10 nm possess high cell viability [216]. There are reports that the solubilizing agents also impacted the toxicity of CNTs [217,218]. Jos et al. reported that –COOH-functionalized SWCNTs induced greater toxicity in the human umbilical vein endothelial cell (HUVEC) cell lines in comparison to the non-functionalized SWCNTs [219]. Metallic impurities such as metal ions incorporated during fabrication contribute a lot to the toxicity of CNTs [220,221]. Graphene also has toxicity concerns that restrict its use in the biomedical field, and to lower it, coating with blood protein has been demonstrated by the Chong group [222]. GQDs with smaller size seems to be less toxic than GO or CNT. Tian and the group reported that hydroxylated GQDs showed substantial toxicity on A549 and H1299 cells [223]. Simultaneously, a study conducted by Nurunnabi et al. stated that carboxylated GQDs showed no acute toxicity on KB, MDA-MB231, A549, and normal cells such as MDCK [224]. They further reported in their in vivo studies that the GQDs did not affect the organs notably in long-term studies.

Garriga et al. reported the cytotoxicity of the various carbon nanomaterials in their study. They developed multiple CNMs such as carbon nanohorns (CNH), carbon nanotubes (CNT), carbon nanoplatelets (CNP), graphene oxide (GO), reduced graphene oxide (GP), and nanodiamonds (ND). They tested the in vitro cytotoxicity of the above-mentioned CNMs by the MTT assay in human epithelial colorectal adenocarcinoma (Caco-2) cells and human breast adenocarcinoma (MCF-7) cells. The cell viability was found to be in the following order: CNP < CNH < RGO < CNT < GO < ND for both Caco-2 and MCF-7 cell lines. They reported that ND and GO showed low toxicity owing to the presence of oxygenated functional groups on their surface, which guards their hydrophobic domains. On the other hand, carbon nanohorns and carbon nanoplatelets induced Caco-2 and MCF-7 apoptosis/necrosis and increased ROS levels, which could be associated with the lowering of cell viability in comparison to carbon nanotubes and reduced graphene oxide [225]. Graphene has been evaluated for its toxicity in animals and cells [226]. A range of animal models has also been utilized in the investigation of e.g., ND biocompatibility and fate in vivo [227]. Various in vitro and in vivo studies have been reported to assess the cell viability, *gene* activity, and physiological behavior of the CNMs [228–232]. In a study on mice, nanodiamonds when administered within the trachea exhibited low

pulmonary toxicity. The amount of nanodiamonds decreased with time in the alveolar region, and the macrophages laden with nanodiamonds stayed in the bronchia for 28 days after exposure [230].

Toxicity issues of CNMs on humans are still not assessed. Few studies have indicated that pristine CNTs, similarly to asbestos, could be the possible source of lung disease in industrial workers [233,234].

Ali-Boucetta et al., in their studies, reported that the asbestos-like reactivity and pathogenicity reported for long, pristine nanotubes can be reduced completely by surface modification and curtailing their length upon reacting with chemicals such as tri(ethylene glycol) (TEG) [235].

By the functionalization of CNMs, toxicity can be lowered for their biomedical applications. Rungrotmongkol et al., in their studies, indicated that non-covalently functionalized chitosan-coated CNTs accumulated in the reticuloendothelial system (RES) and were slowly excreted through the bile without causing side effects to the mice. The so fabricated CNTs displayed improved dispersion and biocompatibility [236]. Similarly, Kam and the group non-covalently functionalized SWCNTs with amphiphilic phospholipid-polyethylene glycol (PLPEG). The developed system exhibited augmented solubility, biocompatibility, and stability in the aqueous phase, as the hydrophobic lipid chains of PLPEG were strongly adsorbed onto the CNTs surface, while the hydrophilic PEG chain enhanced the solubility and biocompatibility of the entire functionalized SWCNTs [237].

Russier et al., in their recent study on myelomonocytic leukemia, reported that few layers graphenes (FLG) dispersions can attack monocytes, being non-toxic to the immune cells. They demonstrated that graphene holds targeting ability and boosted the necrosis of monocytic cancer cells. They further compared the FLG and etoposide chemotherapeutic potential where FLG showed substantial anticancer activity [238].

9. Conclusions

The current market showcases more than 50 nanomedicine-based drug products that are positively affecting the health of humans, and there are hundreds of clinical trials that are ongoing for the treatment of ailments such as cancer, rheumatoid arthritis, inflammatory bowel diseases, and diabetes [239]. Therefore, nanomedicine could be the frontier that could systematically curtail all the toxicity issues to utilize CNMs' potential in biomedical applications.

Carbon-based nanomaterials have established themselves as promising materials within nanomedicine, having found applicability in the potential treatment of many ailments such as cancer, genetic disorders, and the allowed inventive delivery of bioactive. CNTs (single and multiwalled) have displayed excellent carrier properties for the effective delivery of chemotherapeutics, antibiotics, proteins, DNA, RNA, vaccines, *genes*, etc. Graphene derivatives such as functionalized nano-GO have been effective in delivering anticancer agents without affecting healthy cells. The combining factor for the success of CNMs finding their applicability in drug delivery is due to the excellent opportunity of surface functionalization. For instance, the first in vivo transfection example by using a polyfunctionalized fullerene derivative has been recently reported, thus exhibiting their capability in the delivery of nucleic acids. However, toxicity-related issues are to be addressed before and after the CNMs have delivered their payload to finalize their biological fate in the delivery of therapeutics. Although CNMs have immense potential in their application, they have still to find their practical applicability in biomedicine.

10. Future Perspectives

Since the advent of CNMs about 30 years ago, they have established themselves as promising carrier materials in various biomedical sectors such as biosensing, bioimaging, delivery of therapeutics, etc. Despite several advantages, their toxicity concern toward human cells has rung alarm bells for the researchers to seriously monitor this issue. Along with this, their fabrication takes a long time and is expensive, posing a challenge for

large-scale production. Therefore, there is a strict need to find solutions to overcome the challenges of producing non-toxic carbon nanomaterials at a relatively fast pace on a large-scale with low production costs.

Covalent and non-covalent functionalization has paved a way for CNMs to expand their applicability into the biomedical arena, but more has to be done to improve their biocompatibility, i.e., interaction with biological surroundings (cells, or tissues, or organs) and biodegradability or elimination from the body. They are extensively used in aeronautics, space, automobile, textile, sports goods, and so on, yet their applicability on human beings for diagnostics and therapeutic use has not translated from the research laboratory to clinical trials. Their therapeutic use in humans is still waiting to surpass the regulatory hurdle of proving their compatibility, safety, and efficacy. There is a need to develop a systematic nanotechnology-based approach to build an environment for their use in vivo in serious and still largely untreatable ailments such as brain tumors, cerebral stroke, or neurological disorders such as Alzheimer's or Parkinson's.

Future fabrications of CNMs should be amalgamated with some novel intuitive guiding moieties so that they could directly approach the target cells, or the researchers could devise such carbon nanomaterials that could be driven from the outside directly to the affected tissue/organ, thus circumventing the side effects of the CNMs on the neighboring healthy tissues. Functionalization techniques (covalent and non-covalent), modifying the shape and size, use of solubilizing agents, removal of metallic impurities, administration route, coating with polymers, and/or blood proteins, etc., could be the possible answer to improve the raw hydrophobic CNM's solubility and biocompatibility. Their cellular uptake (in vitro) and blood circulation and biodistribution (in vivo) largely rely on surface chemistry. Functionalized carbon nanomaterials with improved solubility, targetability, and biocompatibility could successfully find their way to the clinics for the improved delivery of biomolecules (such as RNA, DNA), small drug molecules, proteins, and peptides. As with any nanomaterials intended for drug delivery, a proper risk assessment evaluation of the toxicity concern of CNM-based delivery of therapeutics is required that should ultimately be extended to clinical trials. An array of safety assessments and in vitro/in vivo cytotoxicity evaluations is the need of the hour to test the effectiveness of the CNMs. Hurdles such as the long-term fate of CNMs should be assessed carefully, and the published data from past studies should be thoroughly screened to bring CNMs further toward clinical translation, to be able to make proper use of the promising applications presented in this review.

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