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Review

A Review on Carbon Nanotubes Family of Nanomaterials and Their Health Field

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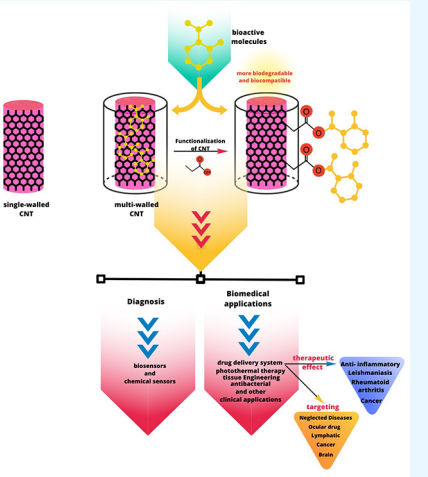
ABSTRACT: The use of carbon nanotubes (CNTs), which are nanometric materials, in pathogen detection, protection of environments, food safety, and in the diagnosis and treatment of diseases, as efficient drug delivery systems, is relevant for the improvement and advancement of pharmacological profiles of many molecules employed in therapeutics and in tissue bioengineering. It has contributed to the advancement of science due to the development of new tools and devices in the field of medicine. CNTs have versatile mechanical, physical, and chemical properties, in addition to their great potential for association with other materials to contribute to applications in different fields of medicine. As, for example, photothermal therapy, due to the ability to convert infrared light into heat, in tissue engineering, due to the mechanical resistance, flexibility, elasticity, and low density, in addition to many other possible applications, and as biomarkers, where the electronic and optics properties enable the transduction of their signals. This review aims to describe the state of the art and the perspectives and challenges of applying CNTs in the medical field. A systematic search was carried out in the indexes Medline, Lilacs, SciELO, and Web of Science using the descriptors "carbon nanotubes", "tissue regeneration", "electrical interface (biosensors and chemical sensors)", "photosensitizers", "photothermal", "drug delivery", "biocompatibility" and "nanotechnology", and "Prodrug design" and appropriately grouped. The literature reviewed showed great applicability, but more studies are needed regarding the biocompatibility of CNTs. The data obtained point to the need for standardized studies on the applications and interactions of these nanostructures with biological systems.



1. INTRODUCTION

Nanoscience and nanotechnology are areas of knowledge and innovation that have aroused increasing interest in the scientific community, since they are conceptualized as a set of techniques used to manipulate molecules on a nanometer scale (10^{-9} m).[1−4] The great interest in the study of these materials is because they present physicochemical properties different from those of the already known base materials, which allows countless new possibilities of applications. These involve the integration of multiple areas of science, including chemistry, biology, medicine, pharmacy, and engineering, with the purpose of promoting quality of life and the promotion of health in society.[2−5]

Various materials have been worked on to the nanometer scale, among them. In the carbon nanotube (CNT) atoms, carbons are arranged in condensed aromatic rings, formed by graphene[5] sheets rolled in cylinders.[6] A sheet of graphene is a 2D structure composed of a network of carbon atoms arranged in hexagonal form and among them by hybridization of their electron orbits, according to the number of layers of graphene.

CNTs, which can also be called pristine, are commercially available in two forms: single layer (SWCNT), with about 0.4 to 2.22 nm diameter, and multilayer (MWCNT), which may vary from 1 to 100 nm diameter (Figure 1).[7] Additionally, the CNT nanoscale diameter makes it attractive, as it provides a large area/volume ratio allowing the use of CNTs as biomolecule carriers, that is, molecules that can interact with cells and tissues.[8−10] MWCNT is the most used for the targeted release of drugs, because of its photothermal properties, due to its ease of absorption.

CNTs have stood out as the most promising nanomaterial in the 21st century with numerous applications,[7] as in tissue regeneration,[10−12] gene therapy,[13−15] and release system,[16] as

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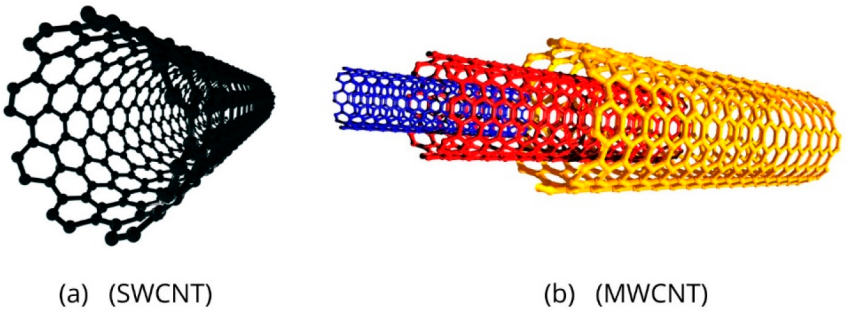

Figure 1. Conceptual diagrams of single-walled carbon nanotubes (SWCNTs) (a) and multiwalled carbon nanotubes (MWCNTs) (b).

it is biocompatible[17] and useful in the detection of tumors.[18−20]

Therefore, it is possible to understand the applications of CNT in medicine and pharmacy, with the field of health being the most advanced.

CNTs should be subjected to chemical treatment through functionalization, adsorption, or binding of either atoms or molecules to their walls or tips. Functionalization makes CNTs more biocompatible and, therefore, facilitates their interaction with organic, biological molecules or with other chemical groups, such as drugs or DNA.[21,22] Moreover, functionalization with the adsorption of chemical groups, such as hydroxylation, makes nanotubes soluble in aqueous medium and facilitates interaction with cell macromolecules.[23,24] In addition, CNTs result in lower toxicity to cells in cultures, thereby increasing its potential for application in biological areas and medical care.[25,26] Furthermore, solubility is an important parameter in making CNTs biocompatible under physiological conditions. The main applications of CNTs in therapeutics[27−29] are shown in the following table (Table 1).

Table 1. Main Applications of CNT in Medicine and Pharmacy

Application	Use
Tissue Engineering	Biomaterial in tissue regeneration
Biosensors	Identification of pathogens
Chemical Sensors	Identification of important chemical indicators and associated with health
Photothermal therapy	Cancer treatment
Drug Delivery System	Transport of pharmacological compounds to specific sites

The development of efficient methodologies used in the functionalization of CNT is very promising for biological and therapeutical applications. There are several methods, which have been used to attach molecules to the walls of functionalized CNT7.[30,31]

The purpose of this review is to describe the state of the art, the perspectives, and the challenges concerning the application of CNTs in the medical area.

2. CARBON NANOTUBES

2.1. Functionalization and Biocompatibility in Pharmaceutical Applications. The diversity of applications or potentialities of CNTs makes the research in this area of knowledge quite multidisciplinary.[32−34] Functionalization is a synthetic process (Figure 3), which is intended to insert functional groups in the CNT walls for various applications, for instance, enhancement of biocompatibility within the body, enhancement of encapsulation tendency, solubility, delivery of drugs, and imaging, among others.[35,36] In this regard, functionalization of CNT (CNT-F) has been outstanding as an excellent tool in the field of nanomedicine facilitating the encapsulation of CNT with biopolymers or by covalent bonds of solubilizing groups anchored in a portion of the CNT wall.[37,38] Additionally, our research group has been studying the best proportion of those acids in the mixture with the aim of increasing the number of carboxyl groups in CNTs. In this case, carboxyl groups are inserted on the surface of CNTs, which increases their dispersibility in aqueous solutions[34] (Figure 2). Thus, CNT-F can be linked to a wide variety of active molecules including peptides, proteins, nucleic acids, and other therapeutic agents.

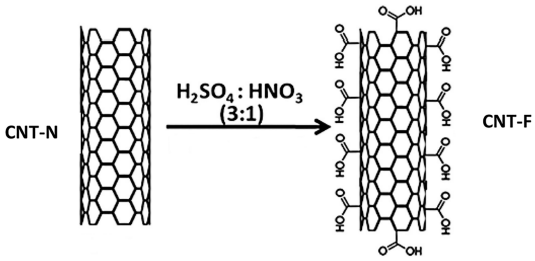

Figure 2. Representative scheme of CNT functionalization, with the incorporation of the carboxylic acid group. CNT-N: carbon nanotube nonfunctionalized and CNT-F: carbon nanotube functionalized.

CNT-F are more soluble and stable in water and serum and have been shown to penetrate mammalian cells, contributing to the transport of biological molecules without affecting their activity.[39,40] Furthermore, CNT-F shows a long half-life in the blood circulation and low absorption by the reticuloendothelial system with absence of side effects, being thus suitable for the process of drug release.[41,42] Hence, the use of nanomaterials as CNT in medical practice is very promising, leading to more refined and efficient treatment.

However, even though a significant number of studies have already highlighted the advantages of medical devices, their clinical use has not yet been completed.[43] Care related to its toxicity, biosafety, and biodegradation remains. The effects of CNTs on the human organism are not well-elucidated, mainly due to a systematicization of toxicological tests that generate controversial results. Thus, the toxicity of CNTs should be further investigated to allow for the use of these materials in medicine in the coming years.

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Therefore, the biological employment of functionalized CNTs is currently under much investigation. In this review, we highlight the most recent approaches of CNTs in different applications in the medical field.

2.2. Application of CNT in Tissue Engineering. CNTs have been showing high applicability for use as biosensors, as they have intrinsic electronic and optical properties which enable signal transduction.[44] Its physical structure, including large surface area and semiconductor property, allows the measurement, detection, or adsorption of biomolecular interactions along the side walls of the CNTs. The proximity of charges or polarized biomolecules produces effects that are propagated over CNTs isolated or arranged in networks, generating a transient field effect that, in its turn, makes it possible to quantify the degree of binding specific or not for biomolecules.[44] Table 2 depicts the use of many different CNTs for tissue engineering.

Table 2. Utilization of Various CNTs in Tissue Engineering

Type of CNTs	Functionalized	Benefits	Ref
SWCNT or MWCNT	Polymers and elastomers	Repair of cardiac tissue and an improvement in the stimulation and electrical conductivity of cardiomyocytes	12
SWCNT	Caspase 3 RNA, F-CNT-siCas3	Early phase of myocardial infarction treatment	45
SWCNT or MWCNT	Silk nanofibrous	Induce the formation of cardiac tissues that mimic native myocardium.	46
SWCN or MWCNT	Biopolymer nanofibers	Tissue healing and bone regeneration	47
MWCNT	Chitosan	Physiological repair of connective tissues	48

(a) Cardiac Tissue. Carbon nanotubes that favor the regeneration of heart cells destroyed after a heart attack, due to a lack of oxygen supply. During *in vivo* experiments, the cardiac tissue was six times denser in the presence of the conductive nanopatch than in its absence, which confirms the patch's effectiveness.[12,45] Made from tiny chains of carbon atoms folded on themselves to form nanofibers, it conducts electricity and mimics the rough surface of natural fabrics. The researchers observed that the higher the concentration of nanotubes, the more efficient the regeneration of heart cells. One of the medical applications of using CNTs is tissue engineering. Work developed by Gorain et al.[12] demonstrates a viable application of CNTs to assist in the repair of cardiac tissue in situations of cardiac tissue death, which corresponds to myocardial infarction. The inclusion of SWCNTs or MWCNTs in fibrous polymeric materials resulted in a remarkable improvement in cardiac tissue repair, promoting an improvement in the stimulation and electrical conductivity of cardiomyocytes. In addition, CNTs allowed improvement in the potential of cell growth, proliferation, differentiation, maturation, and cardiomyocyte functioning. This area is very challenging, as there are great difficulties due to the lack of integration between physical, electrical, chemical, and mechanical properties with cardiac tissue repair substances. CNTs with their appreciable electrical properties help in the transduction of this type of energy through signals to cardiomyocytes, improving the clinical feasibility of myocardial tissue engineering. However, the work indicates that further studies are necessary to make CNTs viable in therapeutics in the repair of cardiac tissue.

In work developed by Li et al.[45] the binding of SWCNT functionalized with Caspase 3 RNA, F-CNT-siCas3, is proposed in order to work as a new alternative treatment option for the early phase of myocardial infarction treatment. *In vivo* studies in mice indicated that this transporter had a positive effect on cardiac function, as it effectively reduced the expression of Capase3 mRNA, which is associated with apoptosis of cardiac cells. In addition, the set showed good water solubility, biocompatibility, and high transfection efficiency of up to 82%. Notwithstanding, there is a need for toxicity tests to complement it.

A study developed by Zhao and co-workers[46] employed CNT matrices functionalized with silk nanofibrous biomaterials to induce the formation of oriented engineered cardiac tissues with enhanced functionalities. The developed CNT/silk composite demonstrated excellent conductivity and mechanical properties through excellent dispersion of CNTs in the composite nanofibers. Furthermore, the compound scaffolds are highly biocompatible and able to promote cell spreading and guide the cellular organization of cardiomyocytes. Nanofiber alignment control for the CNT/silk scaffolds further induces the formation of cardiac tissues that mimic native myocardium.

(b) Bone Tissue. In bone tissue, during the process of bone matrix synthesis and organization of a trabecular system, the collagen triple helices spontaneously form bundles that act as a nucleation site for deposition of hydroxyapatite nanocrystals. Similarly, the structure of carbon atoms gives CNTs a porous three-dimensional plane, which also allows them to control crystal nucleation events and inorganic component growth.[49] Studies have shown that CNTs promote proliferation of osteoblasts and bone formation, therefore representing an enormous technological advancement in the field of bioengineering.[50,51]

Additionally, the association of CNTs with other polymers, whether natural or synthetic, improves the mechanical properties of these polymers,[47,48] resulting in more resistant biocomposites with greater capacity for increased nucleation and growth of hydroxyapatite crystals,[47,48] when compared to the use of polymers in isolation. The literature focuses on the study of CNTs in the research on CNT scaffolds for bone regeneration,[52] Figure 3.

Tissue engineering-based regenerative medicine has been extensively researched for situations that are difficult to treat with existing treatments and large bone defects for which an effective treatment option has not been established.[53,54] The current gold standard for the treatment of large bone defects after tumor resection or trauma is autologous bone graft.[49] However, some notable shortcomings include the limited amount of material available and the pain at the site.[55] Although allogeneic bone is relatively plentiful and can be used for major defects, it can also potentially activate an immune system response and may also present some difficulty in grafting.[56,57] The development of scaffolds is vital to regenerative medicine, and there has been a body of research on the use of carbon nanotubes (CNTs) as scaffolding.[58] Patel and co-workers[47] demonstrated that coating of CNTs with biopolymer nanofibers can modulate multiple cell and tissue interactions that are useful for tissue healing and bone regeneration. This coating significantly reduced the intensity of inflammatory signals and promoted angiogenesis. Further-

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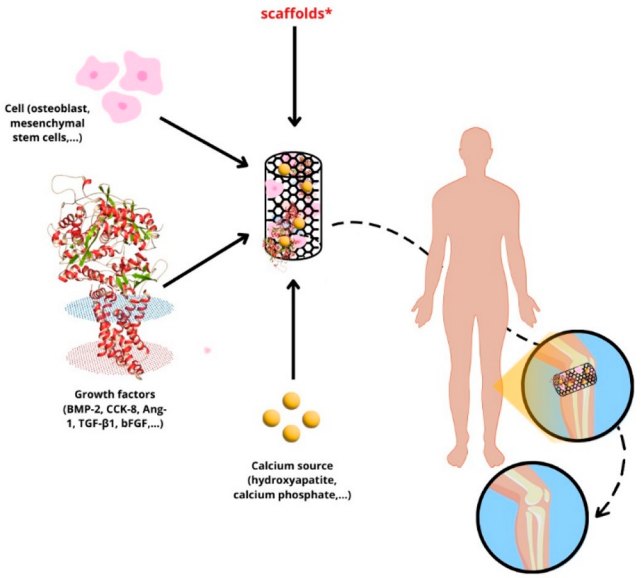

Figure 3. CNT employed in bone tissue. Figure adapted and modified from Eivazzadeh-Keihan et al., 2019.[52]

more, CNT-coated nanofibers increased bone matrix production of bone-forming cells *in vivo* and accelerated the adhesion and osteogenesis of MSCs *in vitro*. These results support the idea that coating biopolymer nanofibers of CNTs is a promising way to promote tissue healing and the bone regeneration process through a series of events orchestrated in anti-inflammation, pro-angiogenesis, and cell-stimulation. Stocco and co-workers[17] performed a study of CNT scaffolds based on polymeric nanofibers with potential application in the treatment of meniscus injuries of the knee. In this case, polycaprolactone fibers aligned with CNT have been used in two different concentrations, 0.05% and 0.10%, with the highest concentration having the best mechanical properties.

In work developed by Kittana et al.,[48] MWCNTs were used together with chitosan, C-MWCNTs, for physiological repair of connective tissues with biophysical properties adapted to the target tissue, denominating optimized engineered connective tissues (ECTs). In this work, one started with human fibroblasts (HFF-1) in collagen type I enriched with three different percentages (0.025, 0.05, and 0.1%) of C-MWCNT. Each percentage showed some advantage, with supplementation with 0.025% C-MWCNT moderately increasing tissue stiffness and supplementation of ECTs with 0.1% C-MWCNT reducing tissue contraction and increasing elasticity and extensibility. It is understood from this work that C-MWCNT supplementation can improve the biophysical properties of ECTs, which may be advantageous for applications in connective tissue repair.

Glass ionomer cements (GICs) are materials with low tensile and shear strength, therefore, being contraindicated for areas subject to large occlusal loads. In this way, the incorporation of carbon nanotubes in the GIC contributes to increasing surface hardness. Another application of CNTs due to their excellent biocompatibility and toughness properties can reinforce any material. As an example, there is the work developed by Goyal and Sharma,[59] in which glass ionomer dental cement is studied. This material, despite having anticary properties and adhesion to a tooth, nevertheless has low mechanical properties. Composites of GIC and multiwalled carbon nanotubes (MWCNTs) were evaluated for potential application as types of dental restorative cements. The composite did not show insignificant changes in temperature and chemical properties compared with the control group. On the other hand, significantly improved mechanical properties were found.

2.3. Applications of CNTs as Biosensors. The construction of biosensors is an alternative in the preparation of electrodes that can provide good results in application in several areas such as healthcare. The advantages of its application are related to its ease of preparation, relatively low cost, versatility, and selectivity. In this case, CNTs are excellent materials for the development of biosensors without clinical analysis. Together with the biological material of interest, these materials can improve the analytical response, promoting the transfer of electrons more easily.

The association between nanotechnology and health care has led to the development of new technologies that are more efficient, faster, and more useful in the diagnosis, treatment, and prevention of any disease. In this range of technologies, biosensors with carbon nanotubes are devices that have been developed and used in recent years, namely, due to their high sensitivity, molecular specificity, speed of analysis, low cost, and ease of use.

This review aims to present, in a general and updated view, some emerging technologies in the form of biosensors with carbon nanotubes that are implemented in the clinical area, mainly for the detection of tumor and in different pathologies which are transmitted by viruses, bacteria, and parasites.[60] Table 3 shows the use of many different CNTs for biosensors, and Figure 4 indicates one approach about CNT as biosensor.

(a) Oxidative Stress. A new electrochemical enzymatic biosensor was designed to evaluate hydrogen peroxide, H_2O_2, which is an important biomarker and is related to oxidative stress. Intracellular or extracellular factors that increase the concentration of H_2O_2 to more than 100 nM interrupt its biological activity and trigger reactive oxygen species (ROS).

Table 3. Utilization of Various CNTs in Tissue Engineering

Type of CNTs	Functionalized	Benefits	Ref
SWCNT and MWCNT	PSA antibody (monoclonal antibody to prostate specific antigen)	Detection early prostate cancer	19
SWCNT	Thionine and gold nanotubes	Detection of Cancer antigen 125 (CA125)	61
SWCNT or MWCNT	Dopamine	Detection early breast cancer	62
MWCNT	PvMSP119 protein	Diagnosis for those infected with malaria	63
MWCNT	Polypyrolle and hydroxyapatite nanoparticles	Diagnostic for those infected with tuberculosis	64
MWCNT	Acrylamide (AAM), *N*,*N*′-methylenebis(acrylamide) (MBA) and ammonium persulfate (APS)	Diagnostic for those carriers of HIVs	65

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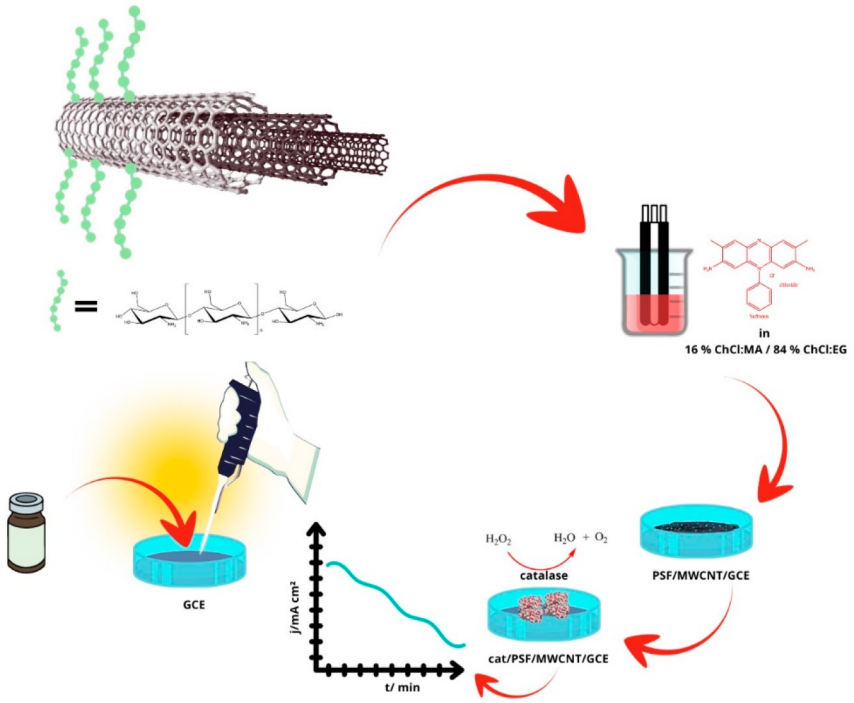

Figure 4. Representative CNT as biosensor. Figure adapted and modified from Zouleh et al., 2023.[66]

The sensor employed a glassy carbon electrode modified with multiwalled carbon nanotube covered by a poly(safranine T) polymer film. Catalase was immobilized on the modified electrode, and the enzyme biosensor was used for measurement of hydrogen peroxide, with a very low detection limit of 34 nM. The selectivity was found to be excellent in relation to common interferences, and the biosensor showed very good recovery in peroxide measurements in commercial samples.[66]

(b) Diagnostic. In the study developed by Ji, Lee, and Kim,[19] multiwalled carbon nanotubes (MWCNTs, diameter 20 nm, length 5 μm) were used as a biosensor to detect early prostate cancer by using a simple carbon nanotube. This device was identified as an inexpensive, simple, and sensitive biosensor, the MWCNTs being bioactivated with PSA antibody (monoclonal antibody to prostate specific antigen) on micropore filter paper (pore size 0.45 μm) by using *N*-(3-(dimethylamino)propyl)-*N*′-ethyl carbodiimide hydrochloride (EDC) and *N*-hydroxysulfosuccinimide sodium salt (NHSS). The prepared biosensor can test from 0 to 500 ng/mL PSA level within 2 h with detection limit of 1.18 ng/mL by measuring resistance. The detection range and sensitivity of the prepared sensor are good enough to diagnose early stage prostate cancer (>4 ng/mL PSA). This biosensor is about 20 times cheaper (manufactured biosensor price: 2.4$) and over 10 times faster than the enzyme-linked immunosorbent assay (ELISA), which is a general method for detecting a specific protein in modernized hospitals. In addition, the maximum detection limit is about 50 times higher than that of ELISA.

Fan et al.,[61] by using a smartphone-based electrochemical system with a differential pulse voltammetry (DPV) measurement, developed a method for cancer antigen 125 (CA125) detection. This antigen is an important tumor marker, which is related to ovarian cancer, lung cancer, breast cancer, and other types of disease.[67,68] This smartphone-based electrochemical system was developed with the combination of the screen-printed immunosensor modified by MWCNTs/Thi/AuNPs nanocomposites, which have been used to immobilize the CA 125 antibody and to perform the differential pulse voltammetry (DPV) measurement for Test CA125, transmitting the detection results to the smartphone via Bluetooth. This system was also evaluated for the analysis of the human serum sample, and the detection results showed good agreement with Roche Electrochemical Luminescence Immunoassay (ECLIA) tests. The proposed system provides a new low-cost, portable method for detecting tumor markers for remote medicine centers in regions with scarce resources.

A stable, unlabeled, ultrasensitive field-effect transistor (FET) biosensor based on a high-purity semiconductor carbon nanotube (CNT) film is reported to detect exosomal miRNA, which is an important potential tumor biomarker.[69] This biosensor named CNT miR-FET was functionalized by DNA, which directly converts the electrical tracking signal caused by the interaction between the biomolecules of the sensor interface into a readable electrical signal, which establishes the basis for detection. Among the great advantages of this biosensor is the ability to distinguish the level of miRNA expression in cancer patients. Furthermore, this device has the potential to be integrated with microfluidic technology to rapidly and ultrasensitively detect multiple tumor biomarkers on one chip, thus achieving accurate tumor diagnosis.

Electroactive carbon nanotubes functionalized with dopamine (DA)/mucin-1 and Ag[62] were used as a signal to generate probes in the construction of electrochemical immunosensors for the early diagnosis of breast cancer. This device served as a support to immobilize the antibody (anti-MUC-1), while the response of functionalized electroactive carbon nanoprobes was used for quantitative measurement of MUC-1. Cyclic Voltammetry (CV) and Electrochemical Impedance Spectroscopy (EIS) were performed to characterize the transduction surface at different manufacturing steps. This device has presented itself as a new simple and low-cost strategy overcoming the problem of biological damage

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involved in applications in the diagnostic area that can serve as a basis for detection of other analytes. Furthermore, this device can be used for monitoring disease progression, which is more challenging than detection.

An amperometry sandwich immunosensor for carcinoembryonic antigen was fabricated using functionalized carbon nanotubes decorated with concanavalin A together with horseradish peroxidase, HRP-Ab2.[70] The carcinoembryonic antibody was immobilized on the gold electrode modified by a cysteine monolayer. This biosensor exhibited high sensitivity, a low detection limit, long-term maintenance of bioactivity, and cost-effectiveness. Thus, the immobilized technique and detection methodology could be developed for clinically interesting biospecies.

The CNT can also be used to recognize other infectious agents, such as protozoa, viruses, and bacteria, in addition to other infectious agents. In a portable microfluidic electrochemical immunosensor for *Plasmodium vivax*, which is the etiologic agent of malaria, antibodies determination was developed by Regiart et al.[63] This device consists of a nanostructured gold surface containing MWCNTs, followed by the immobilization of the PvMSP119 protein, which was applied to human serum samples. This sensor demonstrated better performance than the Elisa assay, in which it had improved sensitivity and accuracy and less assay time (2.5 h shorter) using fewer reagents. Furthermore, this microfluidic electrochemical immunosensor can be used for the point-of-care diagnosis of *P. vivax* malaria in human serum samples.

Paul et al.[71] developed a nanofiber-based chemoresistive biosensor for malaria detection through histidine-rich protein II (HRP2) present in *Plasmodium* sp. The detection platform is formed by the deposition of nanofibers, which contain MWCNTs-ZnO, between the source and drainage electrodes modeled on a thin, flexible poly(ethylene terephthalate) (PET) substrate. This approach creates the functional groups on the surface of the nanofiber that are used for the one-step immobilization of HRP2 antibodies without further surface modification. The device has good sensitivity, a wide detection range, and a specific target for HRP2 antigens. This platform presents itself as an alternative and with great potential that can be used through specific markers associated with the identification of various pathologies.

There are works in the literature in which CNT is used in the recognition of *Mycobacterium tuberculosis* (M.tb). This parasite is responsible for promoting tuberculosis (TB), a disease that is among the 10 leading causes of death in the world.[65] Rizi et al.[64] developed a DNA biosensor using multiwalled carbon nanotubes (MWCNTs), polypyrrole (PPy), and hydroxyapatite nanoparticles (HAPNPs) for highly sensitive and specific recognition of M.tb. The biosensor consisted of an *M.tb* ssDNA probe covalently linked to the HANPs/PPy/MWCNTs/GCE surface that hybridized to a complementary target sequence to form a double DNA. The DNA biosensor exhibits a wide detection range from 0.25 to 200.0 nM with a low detection limit of 0.141 nM. The performance of the biosensor designed for clinical diagnostics and practical applications was revealed through hybridization between DNA probe modified GCE and DNA extracted from clinical sputum samples. This biosensor may serve as a promising screening tool for identifying M.tb at the point of care in an underserved and vulnerable population.

Another electrochemical DNA biosensor was developed by Thakur et al.[72] (2017), in which the identification of the antigen was MPT64 from M.tb. In this platform, the polymer poly(3,4-ethylenedioxythiophene) (PEDOT) doped with carbon nanotubes (CNTs) functionalized with carboxylic groups was used, to which it was bound to streptavidin. The biosensor presented a low detection limit and stability of 27 days at 4 °C and can be reused 7 times after regeneration.

Cabral-Miranda et al.[73] conducted studies with biosensors reported on the Zika virus (ZIKV), which emerged as a global threat after its spread. This virus induces microencephalies and other brain damage, and there are no reliable serological tests capable of distinguishing between ZIKV and other Flavivirus infections, in particular, Dengue virus (DENV). This platform consisted of CNT functionalized with carboxylic groups (−COOH) on the surface of the working electrode, bound with carbodiimide hydrochloride, EDAC, and *N*-hydroxysuccinimide (NHS). Subsequently, the specific antigens NS1 and ED III, corresponding to ZIKV, were immobilized. This device was applied to blood-free antibodies in saliva and found to be highly sensitive and specific for the detection of ZIKV.

A fast, simple, and sensitive method for the determination of the human immunodeficiency virus p24 (HIV-p24) has been developed by Ma et al.[65] Thus, a new electrochemical sensor of molecularly imprinted polymers (MIPs) was constructed on the surface of a modified glassy carbon electrode (GCE) containing multiwalled carbon nanotubes (MWCNTs) using acrylamide (AAM) as functional monomer, *N,N′*-methylenebis(acrylamide) (MBA) as cross-linking agent, and ammonium persulfate (APS) as initiator. The proposed electrochemical biosensor MIPs exhibited specific recognition for HIV-14 with superior performance to most other devices based on other methods for the recognition of HIV-p-24. In these studies, real samples were analyzed in human sera with simple, low-cost, effective, and sensitive determination of HIV-p24 antigen, and this analysis provides promising potential in the clinic.

Lee et al.[74] proposed an immunosensor for the detection of swine influenza virus H1N1, and this assay was based on the excellent electrical properties of SWCNT. For the construction of this film two bilayers of poly(diallyl dimethylammonium chloride) (PDDA) and poly(stylenesulfonate) (PSS) were first self-assembled as a precursor layer in the substrate pattern for charge increase followed by the assembly of (PDDA/SWCNT) as a material electrochemical transducer. In addition, anti-SIV and SIV antibodies were used during the assay. This biosensor demonstrated high selectivity and suggested a potential application of this assay as a detection or monitoring system at the point of care.

Biosensors in CNTs for rapid and highly efficient detection of avian influenza virus H5N1 subtype DNA sequences have also been also developed. In this case, SWCNTs and nitrogen-doped CNTs (N-MWCNTs) were used as two active sensing elements.[75] The lowest concentration of DNA T detected was 2 pM for the SWCNT and 20 pM for the N-MWCNT sensor after 15 min of incubation. This means that the SWCNT-based sensor showed higher sensitivity compared with the N-MWCNT-based devices. No detection response to non-complementary H1N1 DNA was observed. CNT-based DNA sensors are small, flexible, easy to use, and highly sensitive, making them promising in clinical diagnostics as well as for portable applications.

In a further study, Palomar et al.[76] proposed an impedimetric biosensor controlled by layers of CNTs presenting high performance in the detection and quantifica-

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Table 4. Utilization of Various CNTs as Chemical Sensors

Type of CNTs	Functionalized	Benefits	Ref
SWCNT and MWCNT	Mucina	Detection of glucose in human plasma	78
MWCNT	Poly(methylene blue) (PMB)	Detection of cardiac troponin T (cTnT), which crucial cardiac biomarker for the diagnosis of acute myocardial infarction	80
MWCNT	Nanowires and tyrosinase	Detection of catechol	81
SWCNT and MWCNT	Capsaicin	Detection of dopamine (DA), epinephrine (EP), xanthurenic acid (XA), ascorbic acid (AA) and uric acid (UA).	82
SWCNT and MWCNT-F	cobalt phthalocyanine	Detection of artemisinin	83
MWCNT	Hemin	Identification of nitro radical from nitrofurazone	84

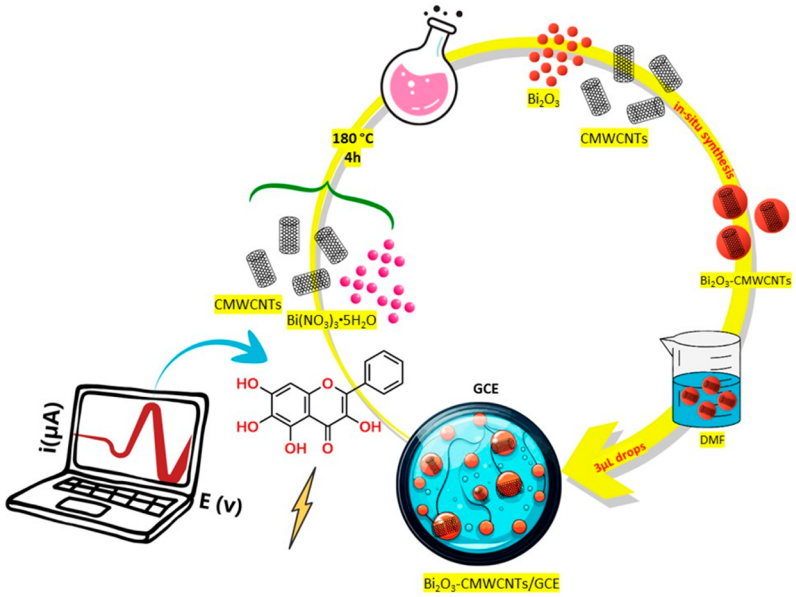

Figure 5. Schematic representation of Bi_2O_3-MWCNTs/GCE fabrication. Figure adapted and modified from Shi et al., 2023.[85]

tion of anticholera toxin antibody. To form the sensor device, the CNT deposits were functionalized via electrocoating of poly(pyrrole-nitrilotriacetic acid) (poly(pyrrole-NTA)) followed by the formation of a Cu(II) complex with NTA functions. The bioreceptor unit, Subunit B of cholera toxin, modified with biotin, was then immobilized via coordination of the biotin groups with the NTA-Cu(II) complex. After optimization, the resulting impedimetric cholera sensor showed excellent reproducibility, increased sensitivities, and a very satisfactory detection limit of 10^{-13} g mL^{-1}. This procedure is currently being studied for other, more sophisticated immune systems in real samples.

Considering what has been reported in previous work, it is important to highlight the contribution of CNT in the rapid and selective identification of a given pathology. This is mainly due to the electrical properties and ability to bind to biological molecules; it is possible to create a perspective on the use of these materials in the diagnosis of COVID-19. Recent studies have also claimed the utility of a specific acidified CNT coupled to RNA lyase with a conversion effect as a likely inhibitor for SARS-CoV-2.[77] Yang et al.[3] demonstrated the acid-sensitivity of coronaviruses toward acidic and higher-temperature environments (above 56 °C for more than 30 min). Thus, CNTs manufactured by acidizing followed by conjugating a special RNA lyase to exploit the capacity of photothermal conversion[78] may prove to be a potential toolkit in the illumination and inhibition of SARS-CoV-2. In this way, CNTs are a promising material in the diagnosis of COVID-19.

2.4. Applications of CNTs as Chemical Sensors. In this part of the work, electronic devices capable of monitoring and quantifying the presence of biologically important descriptors, drugs, and reaction mechanisms are described. Table 4 demonstrates the use of many different CNTs, and Figure 5 indicates one approach of CNTs as chemical sensors.[79]

(a) Monitoring of Drug. Shi and co-workers elaborated a new sensor, bismuth oxide-carboxylated multiwalled carbon nanotube/glassy carbon electrode (Bi_2O_3-MWCNTs/GCE), for monitoring of the flavonoid drug baicalein. In this drug is a flavonoid compound that was originally extracted from the roots of the plant *Scutellaria baicalensis*. It has been found to have various biological effects and properties, such as anticancer, anti-inflammatory, antineurotoxicity, free radical scavenging, and antioxidant effects.[86,87] However, excessive intake of baicalein can cause serious side effects.[88] The method is both stable and effective and was successfully used for determination of baicalein in human urine and the Chinese herb *Oroxylum indicum*.[81]

Pedrozo-Peñafiel et al.[89] studied an electrochemical sensor to quantify primaquine (PQ), which is an antimalarial drug, in which a glassy carbon electrode (GC) modified with MWCNT was used. This modified system promoted an improvement in the analytical signal compared to that observed with the GC electrode. The device allowed for low Limit of Detection

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(LOD), selectivity, and the ability to determine very low levels of primaquine on the order of 250 ng L^{-1}. In addition, they performed a study of recoveries in urine samples, and the results were statistically similar to those obtained by HPLC.

Damphathik et al.[83] successfully developed an electrochemical sensor for the determination of artemisinin (ARN), which is a drug used to combat malaria, in real samples of drugs and plants. The ARN and its derivatives are considered as drugs of first choice for the therapeutic treatment of malaria. One of the major problems faced by society in this area is the adulteration and falsification of antimalarial drugs, which generally contain other drugs or other dangerous impurities.[83] There are many techniques that are employed for the detection of RNA, such as spectrometry,[84] liquid chromatography coupled with tandem mass spectrometry (HPLC-MS),[90] and gas chromatography mass spectrometry (GC-MS).[91] Often these techniques have limitations, such as long analysis time, high consumption of reagents, and need for user training. In this way, electrochemical sensors were employed to effectively detect RNA in antimalarials, mainly focused on the development of alternative methods, because of their many advantages, including high sensitivity, simple use, low cost, rapid detection, and on-site analysis.[83] This same paper proposed a device based on a glassy carbon electrode modified with hybrid nanocomposites of cobalt phthalocyanine, graphene nanoplatelets, MWCNTs, and ionic liquids. The ARN electrochemical sensor provided several advantages such as simple manufacturing, low consumption of reagents and sample, low cost, and short-term analysis. The modified electrode successfully detected RNA content in real samples at reliable and acceptable levels compared with the standard HPLC technique.

Rafati and Afraz[92] developed an electrochemical device to detect zidovudine (ZDV), which is an anti-HIV drug, employing a Ag nanofilm-multiwalled carbon nanotubes modified glassy carbon electrode. The detection and determination of ZDV is of great importance due to its undesirable effects above 10 μM human serum concentrations.[38] This platform showed a low, good sensitivity, accuracy, and fast response to the ZDV and shows an average recovery of 98.6% in real samples.

(b) Monitoring of Glucose. In a paper developed by Comba et al.,[78] an amperometry enzyme electrode was prepared with glucose oxidase, which was immobilized by a cross-linking step with glutaraldehyde in a mixture containing albumin and a new carbon nanotube-mucin compound (CNT-muc). The new CNT-muc compound provided a sensitivity of 0.44 ± 0.01 $mA{\cdot}M^{-1}$ and a response time of 28 ± 2 s. These values were, respectively, 20% higher and 40% shorter than those obtained with a sandwich biosensor prepared without CNT. This device showed good repeatability, reproducibility, and intraday stability in the presence of standard glucose solutions but also was useful for the analysis of real blood plasma samples. Considering that this platform has demonstrated long-term stability under storage conditions of use, it indicates that it can be employed for glucose assessment in a real biological system. These results are very interesting, as it may be a more viable alternative suitable for glucose determination in diabetic patients, as it represents a very economical, robust, and highly sensitive platform for glucose quantification in complex samples.

(c) Diagnostic. Phonklam et al.[80] proposed an electrochemical sensor capable of early diagnosis and follow-up of patients for the treatment of acute myocardial infarction by monitoring the biomarker cardiac troponin T (cTnT). In this work, an impression polymer (MIP), consisting of poly-(methylene blue) (PMB), was immobilized on multiwalled carbon nanotubes (MWCNTs) modified with electropolymerized polyaniline and cTnT. Due to high sensitivity coupled with specificity, cardiac troponin T (cTnT) has been widely used as a crucial cardiac biomarker for the diagnosis of acute myocardial infarction. This is due to its prominent release into the bloodstream during cardiac ischemia.[81,93] The developed MIP sensors showed excellent sensitivity, selectivity, and binding affinity for the detection of cTnT in a real and diluted sample that integrated with screen-printed carbon electrode (SPCE) has high potential for cTnT point-of-care testing.

(d) Identification of Skin Problems. Kurbanoglu and Ozkan[94] developed a new enzymatic device for the detection of catechol using MWCNTs associated with gold nanowires and the tyrosinase class of enzyme. These enzymes tyrosinases (Tyr) also named phenol oxidases catecholates, phenolate, catechol oxidase, or polyphenol oxidase are extensively found in nature and participate in melanin biosynthesis in the human biological system. Due to overexpression of the pigment melanin, some skin problems can occur, and inhibition of melanin biosynthesis can help treat these conditions. The device showed low limits of detection and quantification in monitoring the concentration of Tyr in a biological system. With this, this device has the ability to indicate whether the treatment for the dermatological problems resulting from Tyr activity is being effective.

(e) Identification of Blood Proteins. Zelada-Guillén et al.[95] produced an ultrasensitive and real-time potentiometric sensing medium of CNT blood proteins. In this work, the ability of the functional hybrid carbon nanotubes/aptamer material to create a new generation of nuclease-resistant aptasensors using the potentiometric sensor to recognize a protein-specific RNA aptamer was demonstrated. African trypanosomes were chosen for this work as a model system in real blood samples containing the target protein. This work is intended to indicate the great potential of this device for real-time diagnostic tests for a wide range of diseases but also for the rapid molecular detection of several proteins.

(f) Identification of Endogens Biological. CNTs can also be used for analytical purposes in an attempt to quantify drugs or important endogenous biological molecules. Thus, work developed by Silva et al.[82] built an electrochemical sensor based on oxidized capsaicin/CNT/glassy carbon electrode (GCE) for the simultaneous quantification of dopamine (DA), epinephrine (EP), xanthurenic acid (XA), ascorbic acid (AA), and uric acid (UA). The proposed sensor is easy to prepare and has analytical characteristics comparable to those of other more complex sensors found in the literature. The analytical curves obtained for XA, AA, DA, EP, and UA showed linear ranges, between 10 and 95, 5−75, 5−115, 50−1150, and 5−70 μmol L^{-1}, respectively. The detection limits were 8.76, 1.95, 1.80, 7.20, and 1.56 μmol L^{-1} for XA, AA, DA, EP, and UA, respectively. This capsaicin/multiwalled carbon nanotubes/glassy carbon electrode-based oxidized platform is reported for the first time and is capable of detecting these analytes at a micromolar level.

(g) Evaluation Free Radicals in Mechanism of Reaction. Another interesting aspect of the application of CNT is in drug reaction mechanism studies. In this application, our work group presents experience with some works published in the

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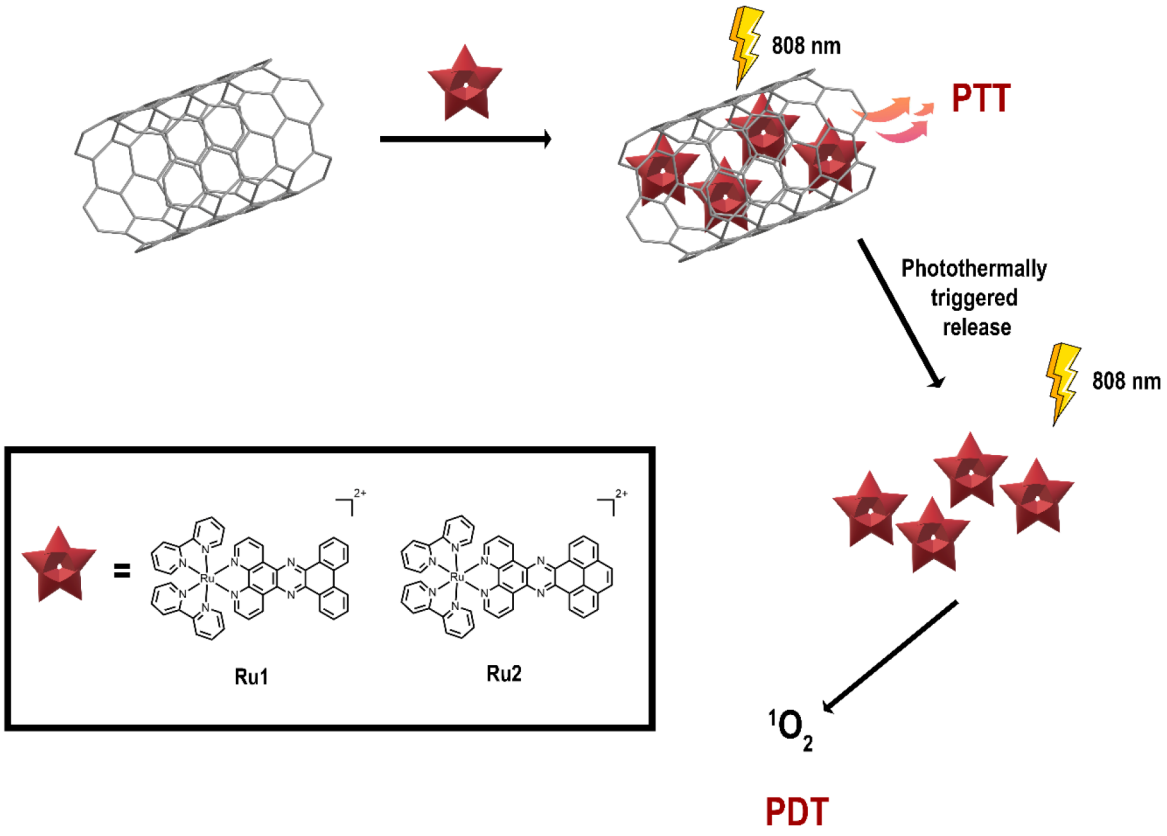

Figure 6. Bimodal photothermal therapy using ruthenium(II) with 808 nm laser radiation. Figure adapted and modified from Zhang et al., 2015. PTT: Photothermal therapy and PDT: Photodynamic therapy.[102]

study of the nitroheterocyclic reduction mechanism using MWCNT functionalized with carboxylic groups immobilized on the surface of a glassy carbon electrode (GCE-CNT-F) to evaluate the reduction behavior of the nitrofurazone (NF),[34] which has antichagasic activity. The biological activity of this class of compounds is dependent on the kinetic stability of the same radical.[34,96,97] The presence of CNT-F did not change the NF mechanism, as it presents the same signs when only the vitreous carbon electrode is used without modification (GCE-SM). However, CNT-F significantly increased the analytical signals of the anionic nitro radical, approximately 140 times higher, and with a potential attenuation of 200 mV compared to the GCE-SM system. The kinetics results showed the longest half-life of the radical, indicating greater stability at the lowest concentration. Another paper developed by our work group was an insertion of hemin together with CNT. It was observed that the synergistic effect among glassy carbon, HEM, and MWCNT in the developed sensor was proven by an electrocatalysis effect represented by reducing the overpotential and increasing the current values, reaching a potential anticipation until 250 mV for the former case and a gain of 40 times in acidic media for the latter.[98]

2.5. Application of CNTs as Photosensitizers in Photothermal and Photodynamic Therapies with CNTs on Anticancer Applications. Even CNTs only functionalized with −COOH already present remarkable photosensitizer effects and potentially can be used for development of Photothermal therapy (PTT) and Photodynamic therapy (PDT).[99] In this regard, in some alternatives, SWCNTs or MWCNTs have been explored as an adjuvant in photothermal treatments due to their light absorber property, being effective against breast cancer in the PTT by development of the CNTs complex with PEG, leading a suppression of tumor growth and reducing the amount of tumor-induced bone destruction[100] and melanoma tumor size after NIR laser radiation.[101]

CNTs were applied in a complex with ruthenium(II) producing reactive oxidative species (ROS) (Figure 6) achieving anticancer efficacies in both *in vitro* and *in vivo* models.[102] Furthermore, CNTs were explored to produce a complex with carbon nanodots (CDs), which presented chemical catalytic activity for H_2O_2 decomposition. In addition, TiO_2 and nanotubes (CDots/TiO_2 NTs) were effective in PDT.[103] Additionally, CNTs nanosystems could be effective in the control of primary tumors and metastases in breast cancer,[104] to efficiently, *in vivo*, promote more than 88.6% EMT-6 cells death at a concentration of 50 μg mL^{-1} under 1.0 W cm^{-2} NIR laser irradiation and present PTT efficiency for *in vivo* antitumor treatment.[105] Moreover, CNTs complexes were used against cancerous bone tumors in a complex of gelatin, akermanite with magnetic nanoparticles of iron oxide leading to a nanosystem with increased adsorption on the surface of bovine serum albumin and less degradation of nanocomplex able to do PTT efficiently killing tumor cells through hyperthermia treatments.[106]

In addition to the source photosensitizer properties of CNTs, these structures can also act as drug carriers. In this sense, many research groups have been studying the chemo-phototherapy properties of CNTs, for instance, against the MCF-7 tumor model using CNTs linked to a photothermal agent (ICG-NH2) and targeted group (hyaluronic acid) as well as attached to doxorubicin (DOX). This has led to

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reduced side effects and improved therapeutic efficacy.[107] In a PTT system using CNTs functionalized with TAT-chitosan as prodrug carrying DOX there is production of a system more sensitive to the redox process from hyaluronic acid.[108] Besides that, CNTs, DOX, and gadolinium have been applied against cancer effectively to accumulate at the tumor site with synergistic antitumor efficacy.[109] In addition, the complex between CNTs with DOX promotes effective MDA-MB-231 cell death by mitochondrial disruption and ROS generation.[110]

Moreover, some agents could improve the nanosystem photosensitizer effect and biocompatibility, where CNTs complexed to poly(*N*-vinyl pyrrole), PEG, folic acid (targeting group), and loading DOX improves water dispersion and biocompatibility and reduces the phagocytosis of the reticular endothelial cells;[111] PEGylated CNTs linked to a metformin promote low dosage 1/280 of typical monotherapy,[112] and CNTs were used in colon cancer studies complexed to hyaluronic acid and chlorin e6 able to act as a PDT agent and drug carrier promoting an enhanced apoptosis of the cancer cells.[113] Additionally, new therapies for cancer treatment are constantly being developed. Therefore, the use of CNT in PTT and/or PDT combined with probes leads to the construction of theragnostic agents. Table 5 demonstrates the use of many different CNTs in photodynamic therapies.

Table 5. Utilization of Various CNTs in Photodynamic Therapies

Type of CNTs	Functionalized	Benefits	Ref
SWCNT and MWCNT	Indocyanine green and hyaluronic acid	Fight against breast tumor	111
MWCNT	Manganese dioxide and poly(ethylene glycol)	Acting as a lymphatic theragnostic agent	111
MWCNT	Poly(ethylene glycol)	Treatment of melanoma	114

In this way, CNT was used against human squamous cell carcinoma by combining indocyanine green (probe) and hyaluronic acid. This complex was used to produce a nanosystem capable of promoting a synergistic action by PTT and PDT in a breast tumor model.[111] The result was more efficient tumor suppression and increased blood circulation time.[110] Another interesting application is the use of CNT with manganese dioxide and PEG acting as lymphatic theragnostic agent. In this work, there was efficiency of tumor action by ablation of tumors using a synergistic PTT and PDT.[111] In pancreatic cancer studies CNTs were able to have activity when combined with conjugate dye (CY7) linked to targeted antibodies (anti-IGF-1R)[111] (Figure 7).

The applications of CNTs in different and promising nanosystems for the treatment of tumors were described. In this regard, CNTs have been reported to be effective in targeting and killing cells, such as melanoma, using antibody conjugates and papillary thyroid cancer. Additionally, PEGylated CNTs could prolong blood-time circulation and improve the biocompatibility of nanosystems. In this regard, CNTs complexed to a PEG derivative and chitosan nanoparticles to target cancer tissue lead to a PDT and PTT agent. Both present with physiological good stability and the conversion of surface charges after exposure to tumoral acidic pH to promote dePEGylation.[114] The PEGylated CNTs targeted with CREKA peptide with affinity for fibrin could, in vivo, accumulate in tumor tissues about 6.4-fold higher than control.[114]

Furthermore, with the medical technological advance, gene therapies are promising for cancer therapy, mainly due to their high selective potential. The use of CNTs in PTT and/or PDT combined with gene therapy has been described, for instance, in the development of a CNTs complex with the expression vector pCMV-GFP (a green fluorescent protein) containing a cytomegalovirus (CMV) promoter. This system is able to activate the promoter-based NIR-responsive RNAi system Hsp70B′ (effective against malignant tumor cells and human breast cancer).[114] In another paper where CNTs were lipid-coated to siRNA and against MRC-5 cells model, the CNTs were able to lead tumor inhibition both in vitro and in vivo.[114]

Another type of CNTs is the carbon nanotube ring (CNTR), which can also be used in the PTT. Song and colleagues developed a gold-CNTR nanocomplex, with photoacoustic imaging agent, able to act as theragnostic agent and tumor inhibition both *in vivo* and in a U87MG *in vitro* cells model.[115]

(a) CNTs in Antibacterial and Other Clinical Applications. CNTs photoconvert near-infrared (NIR) to heat efficiently, as well as some nanomaterials such as polypyrrole (PPy) that present high conductivity properties and photothermal conversion. In this regard, Tondro and colleagues[115] investigated the photothermal and photodynamic potential of a nanocomposite of polypyrrole on MWCNTs (PPy-coated CNTs) as a bactericidal agent. Additionally, the bactericidal effect could be related mainly to oxidative stress and membrane injury by production of heat and a high level of ROS.[116]

In different ways, CNTs have been explored to overcome the resistance of microorganisms to treatments as well as to obtain novel treatment protocols. In this regard, CNTs used in the PDT triggering the CNT interaction with bacterial cells in the presence of visible light led to the *Staphylococcus aureus* cell membrane damage;[117] toluidine blue, a cationic photosensitizer, complexed to CNTs could be used in the PDT against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[118]

Furthermore, CNTs can be used to treat some inflammatory conditions such as chronic inflammation and progressive plaque lesions of arteriosclerosis by photothermal ablation. For this purpose, CNTs were complexed to phenoxylated dextran, making them selective for inflammatory macrophages, which are involved in these processes.[119]

2.6. Carbon Nanotubes: Applications as Drug Delivery System. Several platforms for drug delivery have been developed to improve the efficacy and selectivity of drugs and bioactive compounds, with different approaches such as prodrug design, nanocapsules, nanofluid, and targeted drug delivery systems, among others[120] (Figure 8).

Targeting groups are employed to increase the selectivity of drugs for specific cells, tissues, or diseases. It has been an effective tool in the treatment of pathological disorders, as it can increase the chemotherapeutic effect and decrease the toxicity in normal tissues. Therefore, CNTs have been explored in this field since drugs can be encapsulated within CNTs forming complexes or conjugates on their surfaces through covalent bonds that promote drug release.[121]

As those nanocarriers are alternatives that can be used in drug delivery platforms, in this review we describe the use of CNT in this area, with emphasis on controlled and targeted drug delivery.[122−124]

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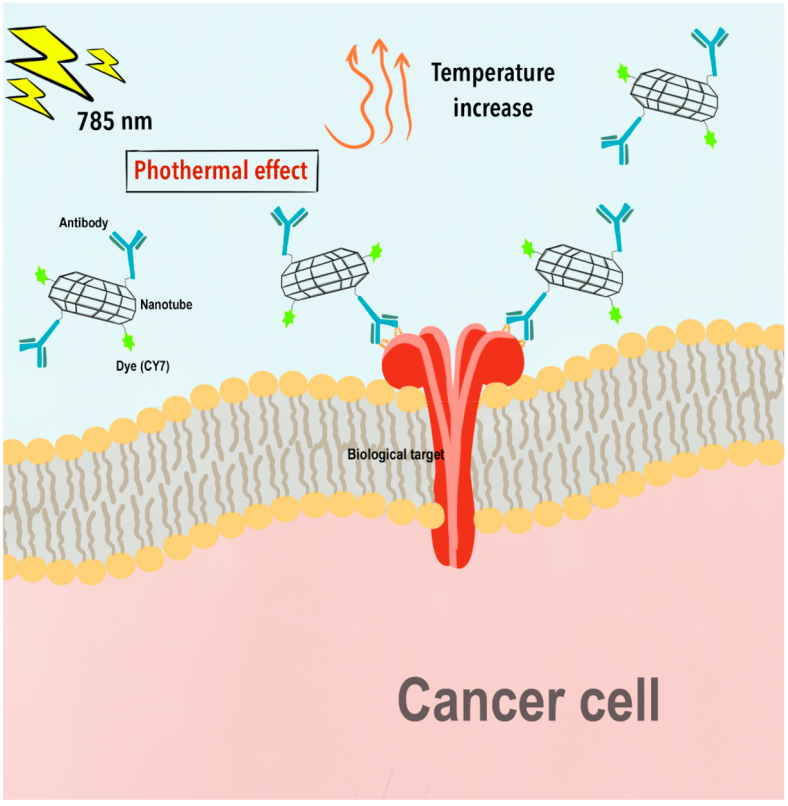

Figure 7. CNTs combined with conjugate dye (CY7) linked to targeted antibodies.

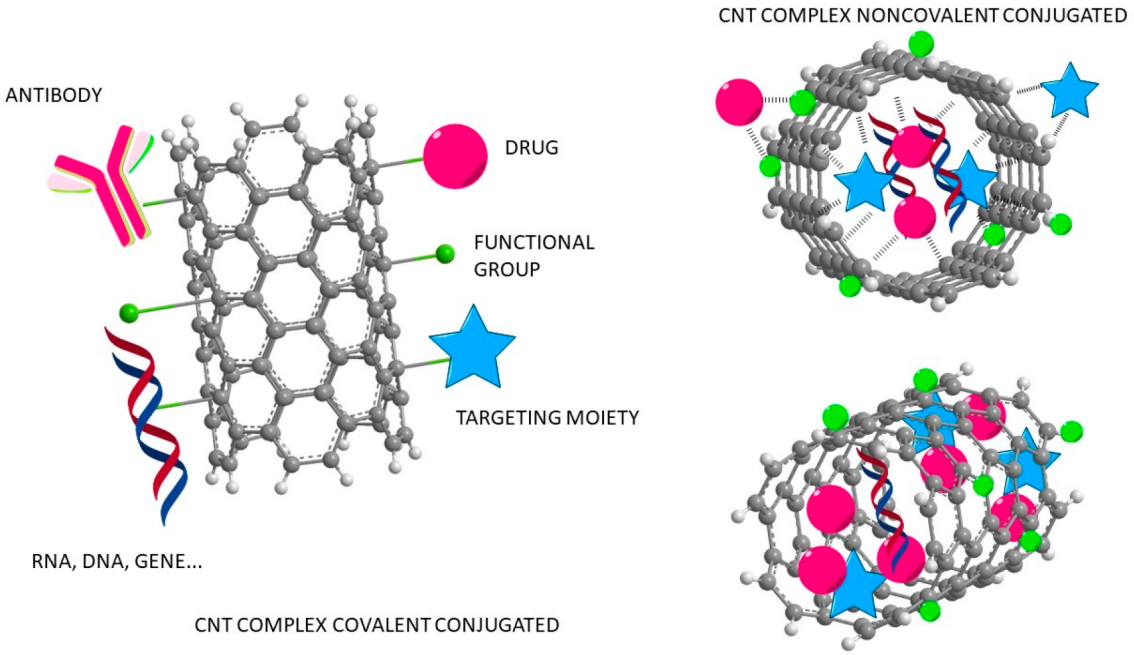

Figure 8. Approaches employed in CNT drug delivery systems.

(a) CNT Prodrug Approaches for Delivery. The nature of carriers for prodrug design represents a challenge, which must be faced in order to aid the drugs to cross the different physiological and physicochemical barriers toward a better activity.[125]

In the last years, CNTs have aroused much interest, mainly in the scientific area, because of their nanometric dimensions and unique structure. They have great potential in medicine, being biocompatible, and have been considered as a tool for the delivery of biologically active molecules and drugs.[126,127] CNTs appeared as the new nanocarriers in drug delivery systems and biomedical applications, and therefore, they can be used in prodrug design to solve problems of drug/bioactive

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Table 6. Different Types of Carbon Nanotubes Explored in Drug Delivery

Pathology	Drug	Type of CNT	Benefits	Ref
Cancer	Cisplatin	MWCNT-F	Reduction in the cell viability of the MDA-MB-231.	142
	Cisplatin	MWCNT-F	Reduces the uncontrolled spread of toxic drug molecules during circulation in the bloodstream and magnetically targeted site-specific release.	144
	Combretastatin (CA4)	SWCNT-F	The anticancer activity of SWCNT combined with combrestatin was improved in comparison with the free drug.	134
	Curcumin (CUR)	SWCNT-F	Ease of loading of hydrophobic CUR molecules, increased biodistribution in cancer cells and good stability against A549 cells.	135
	Curcumin	MWCNT-F	The drug delivery system PVA-MWCNT promoted better release.	137
	Doxorubicin	MWCNT-F	Exceptional colloidal stability, good biocompatibility, high affinity for cancer cells, strong chemotherapeutic performance, decreased side effects and increased antitumor effect via exquisite, targeted drug delivery.	141
	Paclitaxel	MWCNT-F	The dual functionalization of MWCNTs showed better aqueous dispersity and biocompatibility.	140
	Paclitaxel (PTX)	SWCNT-F	Effective inhibition of cell proliferation and death of cancer cells of the A549 lineage and low toxicity.	141
Anti-inflammatory	Ibuprofen	MWCNT-F	Controlled release of ibuprofen and low toxicity.	139

compounds. Literature data indicate that CNTs are flexible carriers because of their ability to overcome cellular barriers.

Prodrugs are molecules obtained by binding the prototype drug/bioactive compound to a carrier, making it inactive or less active, and which, by chemical and/or enzymatic reactions, undergo hydrolysis, releasing the drug.[126,127]

The improvement of the properties of a drug by a prodrug design process should consider some criteria, such as the existence of functional groups capable of undergoing reversible derivatization; the existence of mechanisms in the organism able to bioactivate the prodrug; facility and simplicity of the synthesis and purification of the prodrug; chemical stability of the prodrug; regeneration, *in vivo*, of the parent molecule in ideal amounts. In addition, the drug carrier must have low toxicity.[128−132]

The bond between drug/bioactive compound must be reversible, and it depends on the chemical groups available in the parent drug/bioactive compound. This and the purpose of the designing allow one to choose the proper carrier, which must be nontoxic, in principle.[128−132]

A rapid progression of nanomaterials in the medical and pharmaceutical fields has stimulated their use in the diagnosis and treatment of various pathologies.[133] Several drug delivery studies have used CNT as a carrier agent. The studies mentioned have sought to promote therapeutic guidance and diagnosis.

The main rationale behind using CNT for drug delivery lies in maximizing the biological activity of potent drugs and reducing their side effects and toxicity. Therefore, CNT appears as a promising nanomaterial applicable in studies of drug delivery in the fight against diseases such as cancer and other fatal diseases.[134−143] Table 6 shows some of the applications of CNTs carrier agents in studies of drug delivery.

CNT complexes are formed between oppositely charged particles (e.g., CNT-polymer, CNT-drug, CNT-moiety, and CNT-drug-polymer). CNT complexes involve electrostatic interactions between polyions, dipoles, and hydrogen bonds. This avoids the use of cross-linking chemicals and agents as well as possible toxicity and other reagent effects.[145,146]

An interesting approach is the use of nanotubes as drug delivery nanocapsules, as they have the property of transporting an encapsulated drug to a specific target and ejecting it. This system is known as "magic bullet", and the suction energy must be determined from the radius of a CNT, which will provide the amount of drug absorbed by a determinate nanotube.[147,148] Paul Erlich, at the beginning of the 20th century, proposed the concept of "magic bullet" for nanocapsules[147,148] to provide a more effective treatment, a low toxicity, and to reduce adverse drug reactions (ADRs).[147−149]

The use of CNT has been prominent in the biomedical area mainly because it presents an improvement in the dispersibility in biological means. Surface functionalization is a key element for CNT studies as it promotes the reduction of toxic effects and confers selectivity for a previously established molecular target.[145,150]

CNT has low solubility in water, a limiting factor for its use for drug delivery systems; the functionalization of CNT surface increases the solubility and favors the formation of a complex between the drug and functionalized CNTs through electrostatic interactions.[145]

Previous studies have indicated biodegradation mediated by the oxidation process by CNT functionalization, which occurs in isolated microglia cells. These observations support the use of CNT as a delivery agent for several drugs, among them the anti-neoplastic ones. These results demonstrated the importance of surface chemical functionalization toward the development of CNT to increase their biocompatibility and biodegradability for future biomedical applications in the CNS.[151,152]

The energy interaction between CNTs and cisplatin (anticancer) shows that the radius of the nanotube must be higher than 4.785 Å and that the suction energy peak appears[149] with a radius of 5.27 Å. The ultrashort SWCNTs (US-Tubes) are derived from the SWCNTs by a fluorination and pyrolysis method. This type of CNT is also an excellent candidate for a nanoencapsulation system, as these CNTs fulfill the *in vivo* release of drugs, improving properties such as cellular absorption, and avoid the reticuloendothelium system.[149]

As already mentioned, nanoencapsulation occurs through suction energy, but defects in the walls of the CNTs can also contribute to the drugs entering.[147−149]

Another approach explored is the nanofluid system containing CNT, which may be an injectable suspension and should meet the same conditions as other injectable drugs. Conditions such as particle size control, syringeability, sterility, zeta potential, and pyrogenicity are essential for the safety of injectable drugs.[153]

Theoretically, nanofluids are liquid suspensions containing nanoparticles having a size of less than 100 nm, and the

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employment of CNTs in these systems becomes useful since the particles in a suspension cannot provide tissue toxicity or blockage of blood vessels.[154] They emphasize the use of MWCNT as targeting for tumors in intravenous chemotherapy for its greater mechanical resistance.[153,155]

In order to use the CNTs in a nanofluid system for drug delivery the capillary forces must be checked to understand the interaction between the liquid carrier and the CNTs.[156−158]

Chitosan (CH) is a cationic polymer derived from chitin and is the second most abundant polysaccharide in nature. It is biodegradable, biocompatible, and nontoxic and can lead to specific release properties.[159−161] Exploring such properties, hydrophobic drug loading systems encapsulated within chitosan-based nanoparticles have been extensively studied in recent years, presenting promising results. In a study developed by Dramou and colleagues[161] camptothecin, which is an antineoplastic, was covalently linked with CH, folic acid, and CNT oligosaccharides in order to increase intracellular cellular uptake and also to promote controlled release of the drug. A folate complex was employed to target the conjugate selectively to the cancer cells that express the folic acid receptor. The results *in vitro* demonstrated that the release of camptothecin at pH 5 was greater than at pH 6.8 and 7.4. Moreover, in MTT assays this conjugate showed greater inhibition in the cell growth of colon cancer cells.

Furthermore, Mohapatra and colleagues[162] developed another study using the CH complex together with CNT. The results indicated this complex promotes significantly greater *in vivo* transfection than CH alone as well as increased DNA and peptide transfer into cells.

Rathod and collaborators[140] promoted a dual functionalization on the CNT surface using ethylenediamine (EDA, which is a cationic unit) and phenylboronic acid (PBA, a lectin mimetic) complexed with paclitaxel (PLX). The use of EDA is justified as studies have shown excellent affinity for sialic acid residues (AS), which are negatively charged in the extracellular domain in colon cancer cells. PBA stands out as a portion of the recognition, allowing greater selectivity to target cells. In the release studies, phosphate buffer (pH, 6.8) containing 20% acetonitrile was used as the release medium. The comparison between PLX with functionalized CNT and pristine samples was promoted. The results were very close, with a release rate of about 40% at the end of 24 h. Among the factors that did not allow a greater release are the difference in tube diameter and length and the high affinity between the tube wall and the PLX. Further studies will be conducted by this research group to increase the percentage of PLX release.

(aa) Lymphatic Targeting. The lymphatic system protects the organism against foreign macromolecules, viruses, bacteria, and other pathogens and eliminates altered cells and aged or damaged blood cells.[78] Some types of cancer can travel to other parts of the body through the bloodstream or lymphatic vessels through the metastatic process. Thus, the lymphatic system exerts an important function in the fight against cancer,[163] and the lymph nodes become a potential target in studies on cancer chemotherapy.

Ji and co-workers[163] synthesized the CNT complex previously functionalized with poly(ethylene glycol) (O-mMWNRC-PEG), exhibiting magnetic properties, linked to doxorubicin. This CNT presents excellent adsorption and the ability to target lymphatic system cells. In this study, the authors compared the *in vitro* and *in vivo* activity of the doxorubicin conjugated with the multiwall magnetic nanotube with the drug itself. Experiments *in vitro* demonstrated that the conjugate was effective in inhibiting the growth of breast cancer EMT-6 cells. Furthermore, studies *in vivo* showed the conjugate was in the vicinity of the tumors, promoting the release of doxorubicin for a long period of time, also inhibiting the growth of breast cancer cells.

In studies developed by Yang et al.,[164] the MWCNT complex was functionalized with folic acid and coated with a layer of magnetite nanoparticles and an inner surface loaded with cisplatin through nanoprecipitation. With the help of an external magnet, the cisplatin delivery system was migrated to the lymph nodes, while folate functionalization was responsible for recognition and internalization in tumor cells, thereby demonstrating the controlled release of cisplatin into HeLa cancer cells.

(ab) Brain Targeting. There are many pathologies related to the brain, such as Alzheimer's disease, Parkinson's disease, and stroke, among others, which are prevalent, and the drugs used present low efficacy in the treatment. Many of these difficulties are mainly associated with the blood-brain barrier (BBB), which is impermeable, and the release of drugs is very limited. Thus, release systems employing nanomaterials are considered promising and versatile for the central nervous system because they can overcome such limitations comparatively to the drug itself.[165] Among these nanomaterials used in medicine, CNTs, including both SWCNTs and MWCNTs, have attracted tremendous attention due to their excellent aspects in surface area, electrical conductivity, and biological properties.

In studies conducted by Kafa et al.,[166] they synthesized the MWCNT-F conjugate with angiopep-2, a ligand for low density lipoprotein receptor (LRP1)-related protein-1. This compound showed promising results being radiolabeled to facilitate quantitative analyses by crystallography. *In vitro* assays demonstrated that the conjugate increased BBB transport compared to its equivalents individually. Furthermore, in experiments *in vivo* and after intravenous administration, the conjugate showed a significantly greater brain uptake.

A conjugate between an MWCNT functionalized and a peptide was intended to penetrate the intracellular medium in the treatment of orthotopic glioma. This conjugate was synthesized by You and co-workers[167] and showed a reduced toxicity and also an increased recognition of cancer cells, BBB penetration, and increased anticancer activity due to the production of ROS, as observed.

MWCNTs conjugated with berberine for the treatment of Alzheimer's disease was also studied.[168] Berberine has biological activity and is used in therapeutics in the fight against dementia and other neurological disorders. The conjugate showed an increase in drug absorption in the brain when compared to the pure drug, with potential amyloid reduction induced by Alzheimer's disease.

(ac) Ocular Drug Targeting. An ocular system has many anatomical and physiological barriers, which makes the delivery of drugs very difficult. For this very reason, ophthalmic drugs do not reach the target.[169] Conventional ophthalmic formulations are easily drained, but prodrugs with nanomaterial as carriers allow the prolonged delivery of drugs and the interaction with cornea.

Lu and co-workers[170] studied the cytotoxicity and genotoxicity of plasma-modified MWCNTs, including hydroxyl MWCNT (MWCNT-OH), MWCNT carbonyl (MWCNT-COOH), and MWCNT pristine with human ocular cells, such as retinal epithelial cells. Analyzed by transmission microscopy

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(TEM), all those nanomaterials were able to cross membranes without damaging the cells, as proven by few morphological changes observed. MWCNT−OH exhibited better biocompatibility compared with other materials. The level of cellular apoptosis was less than 1.5%, and the release occurred after 72 h without damaging the cells. This material can be considered as a potential carrier for ocular genetic diseases.

However, regarding this topic there are few studies so far, and therefore, CNT research on the release of drugs into the ocular system should be more explored, considering its potentiality.

(ad) Neglected Diseases. Drug delivery systems employing nanoparticles seem to be a new area in neglected disease (ND) research, which comprises a group of 17 parasitic infections that are endemic in many developing countries. However, it was possible only to verify the use of the CNT against leishmaniasis.

Leishmaniasis is caused by *Leishmania* protozoan parasites and affects over 10 million people in more than 90 tropical and subtropical countries in the new and old world.[171] Human infection is mediated by about 21 species of *Leishmania* parasites. There are at least three different forms of leishmaniasis.[172] Visceral leishmaniasis is the most fatal infection. Nowadays, available treatments are very toxic and very expensive. To face this challenge, CNT can be used because of its ability to easily circumvent cell membranes, acting on multiple targets, and for its biocompatibility. It is reported by many groups that surface-functionalized CNTs are capable of reducing the toxic effect[173] and also increaseing the biocompatibility,[174] thus providing a potential nanoparticle in drug release studies.

Saudagar and co-workers[175] reported the synthesis of a conjugate between CNT-F with a chain of carboxylic acids and betulin (BET), which is a pentacyclic triterpenoid. The conjugate provided a slow release of betulin. The IC50 for betulin and CNT-betulin against intracellular *Leishmania donovani* amastigotes was 8.33 ± 0.41 and 0.69 ± 0.08 μg/mL, respectively, which shows an increase in the activity. The cytotoxicity assay was performed on the J774A1 macrophage cell line, being 211.05 ± 7.14 and 72.63 ± 6.14 μg/mL for betulin and CNT-betulin, respectively. Thus, the results demonstrate better antileishmanial efficiency of the CNT-betulin conjugate than betulin alone, with no significant cytotoxicity observed on host cells.

Studies employing SWCNT and MWCNT conjugated with cisplatin (CP-SWCNT and CP-MWCNT) against *Leishmania major* were performed.[176] This study was carried out to evaluate the cytotoxicity and antileishmanial activity of cisplatin linked to CNT against both promastigotes and amastigotes of *Leishmania major in vitro*. In IC50 assays in promastigote cells, CP-SWCNT and CP-MWCNT were 4- to 7-fold more active than CP and glucantime, which were used as controls. In the studies with amastigote forms, CP-SWCNT and CP-MWCNT were shown to be 11 and 7 times, respectively, more active when compared to control.

(ae) Cancer Therapy. Preclinical *in vitro* and *in vivo* tests showed CNTs as promising nanocarriers for cancer treatment,[41,177−180] but neither FDA approvals nor clinical trials have been reported so far. CNTs, once in the vicinity of the tumor, can: (i) release their cytotoxic content next to the cancer cells; (ii) bind to the membrane of the cancer cells and release their content in a sustained way; (iii) be internalized into the cells.[181]

Moreover, surface modification using cancer cell targeting molecules provides CNTs with enhanced tumor cell specificity, which could overcome the cytotoxicity and the multidrug resistance issues.[182−186] However, concerns over certain issues such as biocompatibility and toxicity have been raised and warrant extensive research in this field.[40]

For example, Yu and co-workers[142] synthesized the paclitaxel (PTX) conjugate with noncovalently associated SWCNTs to CH and hyaluronan to obtain the specific targeting property. The results showed that the release of PTX was triggered at pH 5.5, and a significant improvement in intracellular reactivity with oxygen species (ROS) was observed, which should have increased activation of activated kinase proteins by cellular apoptosis. Cell viability tests indicated that PTX-conjugated SWNT destroyed A549 cancer cells more efficiently than did free PTX.

CNT-F conjugated to the anti-neoplastic drug methotrexate (MTX) employing fluorescent nanoreleasers was studied by Ajmal and co-workers;[187] the studied CCNTs showed promising biocompatibility, and the CNT-MTX conjugate demonstrated a potent cytotoxic effect and carcinogenic activity in a human lung cancer cell line.

Lu and co-workers[170] performed studies using doxorubicin (DOX) conjugate MWCNT, which in turn is conjugated with folic acid (FA) and magnetic nanoparticles (MN), constituting the DOX-FA-MN-MWCNT system. This study addresses the release of DOX in the treatment of two-way cancer cells, with the first being by magnetic orientation and the second by ligand−receptor interactions. Free DOX presented low cell viability due to its low solubility when compared to its complex. In addition, this conjugate showed enhanced cytotoxicity in relation to U87 human glioblastoma cells compared to DOX. Through transmission electron microscopy and laser scanning confocal microscopy, the authors confirmed that DOX-FA-MN-MWCNT can be efficiently absorbed by U87 cells with subsequent intracellular release of DOX followed by going into the nucleus with the nanocarrier left in the cytoplasm. This treatment promoted selective killing of U87 cancer cells at the site of magnetic targeting without affecting the healthy cells used as controls.

3. RISKS AND EFFECTS OF CNTS

CNTs have enabled us to generate nanomaterials with characteristics of unique chemicals, arousing the interest of different scientific areas for their potential applications. Both single-walled and MWCNTs functionalized or not are promising materials for biomedical applications. However, several questions about their toxicological profile should have been answered because many works did not relate. However, one of the restrictions on the use of CNTs *in vivo* is their reduced biocompatibility and poor dispersibility. Furthermore, even today, there are still some points that must be experimentally evaluated regarding the toxicity of CNTs. In this sense, Lemos et al. employed poly(ethylene glycol) chains were covalently linked to MWCNTs (PEG-MWCNTs) through an aliphatic nucleophilic substitution chemical reaction and radiolabeled with 99 mTc. Biodistribution studies were carried out in tumor-bearing mice, and the results revealed that the produced system displays a prolonged blood circulation time and relevant tumor uptake rates. Toxicological data were obtained from testing on healthy animals, and the data revealed that PEG-MWCNTs did not induce an important toxicity profile. Considering all the results obtained

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Table 7. Utilization of Different CNTs in Genotoxicity Studies

Type of CNTs	Test type	Objectives	Conclusions	Ref
SWCNT and MWCNT	*In vitro* (Inhalation and instillation tracheal in rats)	Assess the health risks of inhaling carbon nanotubes	Carbon nanotubes did not interact directly with genetic materials; indicating that the genotoxicity be of the secondary type	195
MWCNT	*In vitro* (Epithelial cells of human lung)	Measuring the genotoxicity of nanotubes carbon	Exposure to each MWCNT led to an increase significant number of mitotic aberrations with morphologies of multi- and monopolar spindle and fragmented centrosomes	196
MWCNT	*In vitro* (Pleural cells human)	Assess cytotoxicity, genotoxicity and cell motility	MWCNT did not affect the proliferation of MeT-5A cells at 10 μg/cm2 within 72 h of treatment, but under the same conditions, MWCNT induced genotoxicity and disturbed cell motility	197

in this work, the PEG-coated MWCNTs can be considered a potential candidate for future oncology.[188] On the other hand, Liang et al. identified that MWCNT exposure was observed to cause damages to the viability of ocular cells; however, the underlying mechanisms remain not well-understood. This study provides the first evidence that DNA hypermethylation in the promoter (cg14583550) and downregulated expression of FANCC gene may be underlying mechanisms associated with MWCNT-induced retinal toxicity.[189]

Due to the variation in structure, size, and chemical surfaces among SWCNTs and MWCNTs[190] the solubilizing agents also have an imperative part in the toxicity of CNTs. In natural dispersants, individual CNTs tend to bundle, which leads to toxicity.[191]

This is possibly due to MWCNT, as the same numerous aspects have been responsible for the toxicity of CNTs; that is, metal impurities in CNTs have a considerable impact on toxicity. Another important aspect that must be considered is the procedure for obtaining CNTs. There are different methods of obtaining SWCNT and MWCNT, and these can generate varied products, with different types and amounts of impurities, which could result in a wide variety of waste. Therefore, to regulate CNTs, agencies must request scientific evidence from manufacturers that their use does not harm public health. One solution to the issue of regulation would be to adapt existing standards.

4. .GENOTOXICITY OF CNTS APPLIED IN HEALTH

The respective review aims to analyze the genotoxicity of the applied nanostructures in health since, although these materials are widely used on industrial and commercial products in the medicinal sector, the potential health risks associated with exposure to them still need to be understood. The possibility of CNTs presenting different actions becomes a challenge in being integrated temporarily or definitively as part of a biological system, since their objective is to restore or replace the function of organs and tissues.[192] In this sense, testing genotoxicity assesses the ability of CNTs to damage the genetic information of cells and cause mutations or induce modifications in the structure of the deoxyribonucleic acid (DNA) of a living organism, even if the damage is not potentially mutagenic or carcinogenic.[193] The way to identify possible chromosomal aberrations is based on increased erythrocyte frequency; polychromatic tests with micronuclei and tests indicating oxidative stress can lead to injuries to cells, in addition to polymorphisms.[194]

Although nanostructures have been widely used, potential health risks need to be addressed; therefore, this review aims to analyze the genotoxicity of nanostructures applied in health. Three studies included in this review evaluated the risks of carbon nanotubes according to *in vitro* and *in vivo* tests, Table 7.

According to the data of Table 6, one of the studies evaluated SWCNT and MWCNT; the histopathological examination detected inflammation in lung cells, including infiltration of immune system cells such as macrophages and neutrophils after the first exposure. The comet test does not indicate tail alteration in the DNA of lung cells exposed to SWCNT and MWCNT. The *in vitro* test of chromosomal aberrations also did not find structural aberrations in DNA. Despite the episode detected, no genotoxic effects of SWCNT and MWCNT were observed in the erythrocyte micronucleus in mammals.[195]

The second paper quantitatively analyzed the chromosome spindle pole of lung epithelial cells, which showed a significant increase in centrosome fragmentation at doses of 0.024 and 2.4 μg/mL of MWCNT and aberrations with morphological changes of the spindle and centromere fragmentation. Cytotoxicity analysis after 24 and 72 h of exposure to MWCNT showed a decrease in cell viability with increasing exposure time regardless of dose.[196]

The third study found that human bronchial epithelial cells exposed to a concentration of 3 μg/mL of MWCNT for 5 days underwent regulation of mitochondrial genes, decreasing intracellular mitochondrial abundance and oxygen consumption, inducing cellular mitophagy two hours after exposure. While MWCNT induced an increase in mitochondrial gene expression, it decreased the oxygen consumption rate and consequently mitochondrial abundance. Although the results were similar at a concentration of 12 μg/mL of MWCNT during the same period, this dose was considered cytotoxic after the fifth day of exposure.[197]

Although carbon nanotubes are a commercially important product, the studies analyzed presented controversies in their results. Nakanishi et al. point out that SWCNT and MWCNT, even at doses that triggered an inflammatory process in rat lung cells, did not show genotoxic potential.[195] Siegrist et al.[196] showed in an *in vitro* analysis that MWCNT caused mitotic and chromosomal disruption in primary human lung cells. In both *in vitro* and *in vivo* tests, MWCNTs were shown to promote genotoxic potential in populations exposed to this type of nanomaterial. Snyder et al.[197] point out that MWCNTs, although not inducing significant mutations in mitochondrial genes, have caused significant regulations and decrease in intracellular mitochondrial abundance. Wu et al.[198] reported in their study that MWCNT induced genotoxicity in cells, mainly those with long-term exposure.

5. CONCLUDING REMARKS

The field of biomaterials sciences is growing, and CNTs have been intensively studied in recent years for several areas. In this Perspective, we highlight biomedical CNT applications based on CNT mechanical and electronic characteristics that can be relevant in several areas.

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Many approaches have been investigated for the application of CNTs such as drug delivery, gene delivery, DNA, RNA, antibody, and steering groups, among others, forming complexes through covalent, noncovalent, or both bonds. In these systems, we highlight their use in the design of sensors, probes, tissue engineering, and photodynamic therapy, among others. CNTs allow us to associate some tools used in drug design with improving the characteristics of these molecules. In addition, it is worth mentioning that CNT functionalization can make CNTs more biodegradable and biocompatible. As we have presented here, it is possible to conjugate the drug and also theragnostic agents with the functionalized CNT and adsorb directing groups in its cavity, reducing toxicity. Nanotubes show themselves as a multiplatform for biomedical applications, and we believe that in the very near future many examples can arise.

Although most studies focus on the area of cancer due to the possibility that these nanosystems target the drug, increasing selectivity and consequently reducing toxicity, which is extremely necessary to improve the therapeutic use of antitumor drugs that usually present significant toxicity, it is also possible to use theranostic agents for imaging and monitoring of treatment. Although the use of CNTs and the diversity of their applications are promising, it is worth mentioning that there is a need for more studies, mainly *in vivo*, to ensure their safety, since there are still divergent data in the literature about their toxicity. In general, toxicological studies involving nanoparticles are still scarce, and their results are controversial compared to each other, mainly due to incipient standardization. The studies are mainly silent on the characterization of particles, contributing little to the understanding of their interaction in the environment and making it difficult to assess the real risk of exposure to these materials. Despite this, most studies indicate some acute toxic effects, which demonstrates the need for a better understanding of the effects of these materials before they are used in everyday processes/products.

The analysis of the risk to human health depends mainly on the regulatory structure, involving the generation of protocols. They must be based on a multidisciplinary interaction, mainly between chemistry, responsible for the synthesis, quantification, and characterization of materials, biology, and medicine, in the design of tests and the interpretation of results in order to obtain a risk assessment in the most reliable way possible. With the increase in research in this area, which includes monitoring CNTs and human health, it will be possible to assess the risk of contamination by these materials through probabilistic calculations. Therefore, new legislation should appear in the near future, indicating guide values for each nanomaterial and situation, in addition to new treatment technologies for this type of waste.

Knowledge of the risks that CNTs cause to people will be important so that the production, commercialization, and disposal of CNTs are carried out appropriately and sustainably. Therefore, in order to sell safe products, the products must comply with the standards required by legislation regarding environmental and public health aspects.

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Notes

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