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REVIEW

Carbon nanotubes in biomedical applications: current status, promises, and challenges

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Abstract

In the past decade, there has been phenomenal progress in the field of nanomaterials, especially in the area of carbon nanotubes (CNTs). In this review, we have elucidated a contemporary synopsis of properties, synthesis, functionalization, toxicity, and several potential biomedical applications of CNTs. Researchers have reported remarkable mechanical, electronic, and physical properties of CNTs which makes their applications so versatile. Functionalization of CNTs has been valuable in modifying their properties, expanding their applications, and reducing their toxicity. In recent years, the use of CNTs in biomedical applications has grown exponentially as they are utilized in the field of drug delivery, tissue engineering, biosensors, bioimaging, and cancer treatment. CNTs can increase the lifespan of drugs in humans and facilitate their delivery directly to the targeted cells; they are also highly efficient biocompatible biosensors and bioimaging agents. CNTs have also shown great results in detecting the SARS COVID-19 virus and in the field of cancer treatment and tissue engineering which is substantially required looking at the present conditions. The concerns about CNTs include cytotoxicity faced in in vivo biomedical applications and its high manufacturing cost are discussed in the review.

Keywords Biosensors · Reproducibility · Functionalization · Toxicity

1 Introduction

Carbon is one the most versatile element and has several allotropes and structures with various properties because of their *sp*, sp^2, or sp^3 hybridization. These properties allow the formation of diverse structures ranging from a few nanometers to hundreds of millimeters. Carbon materials that can be synthesized and characterized at the nano-level have become a center of attraction in the field of nanotechnology. Carbon nanomaterials have unique properties such as high specific surface area, high carrier mobility, higher electrical conductivity, flexibility, and optical transparency; hence, they find applications in a variety of the areas such as drug delivery, biosensing, molecular imaging, and tissue engineering [1]. Various structure can be molded from carbon nanomaterials such as nanowires, 2D films, and a range of 3D structures. Carbon-based nanomaterials comprise fullerenes, graphene, carbon nanotubes, and their derivatives such as nanodiamonds [2], graphene oxide, and carbon-based quantum dots [3, 4]. In 1991, Iijima discovered carbon nanotubes (CNTs), which captivated the interest of many people due to their outstanding electrical, optical, thermal, and mechanical properties and is considered as most distinctive invention [5, 6] in nanotechnology. The CNTs are formed by layers of carbon atoms mounted on each other in a rolled tube, in a hexagonal shape. CNTs have an arrangement of sp^2 hybridized carbon atoms with an interatomic distance of 1.4 Å. CNTs are also known as buckytubes which are hollow tubes with diameters in the nanometers range.

CNTs are usually divided into two types based on the number of carbon layers present. Single-walled carbon nanotubes (SWCNTs) which comprise a single layer of graphene have diameters ranging from 0.4 to 2 nm and mostly occur as hexagonally packed bundles. The SWCNTs have two regions that have distinct physical and chemical properties. The two regions are the sidewall of the tube and the end cap of the tube [7]. Multi-walled carbon nanotubes (MWCNTs) have a complex structure that consists of two or more cylinders

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(approximately 50), each made up of graphene sheets. The diameters are in the range of 1–3 nm [8]. They can also be defined as the concentric arrangement of multiple SWCNTs. MWCNTs have been used in wide areas such as high-frequency semiconducting devices, light-emitting diodes (LEDs), microelectronic devices, wearable, and textile-based electrodes, large-area printed electronics, radio-frequency identification (RFID) tags, circuits, humidity sensors, catalysis, and flexible sensors for measuring bio-signals such as electroencephalography, electrocardiogram (ECG), and electromyography [9]. MWCNTs show superior mechanical and physical properties which include a high modulus of elasticity (≥ 1 TPA), a tensile strength of 65–93 GPa, twice the thermal conductivity as that of diamond, a high aspect ratio in the range of 100–2,50,000, excellent electrical conductivity and are mostly present as a fluffy black and granular powder [10–12].

CNTs have a very simple chemical composition and atomic bonding configuration but manifest an extreme richness and variety in their structures and structure–property relations. Properties of CNTs can vary depending upon its length and diameter. The electrical properties of the carbon nanotubes can be easily altered by introducing the trivalent or pentavalent impurities into the nanotube structure. These dopants can occupy the intershell spaces in MWCNTs or the cylindrical voids in SWCNTs [13]. CNTs possess a very high thermal conductivity (at 300 K it can be in the range of 3000–6000 W/m.K) as a result of the strength of the atomic bonds [14]. It can withstand high temperatures (750 °C at normal and 2800 °C at vacuum atmospheric pressures). CNTs have a high density ($\rho \leq 1600$ kg/m^3), specific heat (425 Cp (J kg^{-1} K^{-1})), and tensile strength (22.2–63 GPa). Its thermal conductivity is dependent on its surrounding temperature as well the temperature inside it. CNTs are stiffer in comparison to a diamond and exhibit a maximum tensile strength of around 100 GPa and Young's modulus of 1.4 TPa [15].

SWCNTs and MWCNTs differ in some aspects from one another. SWCNTs consist of a single graphene layer and can be twisted easily, while MWCNTs have multiple graphene layers and are difficult to twist. MWCNTs can be synthesized without a catalyst, but that is not the case for SWCNTs. Bulk synthesis becomes easier for MWCNTs, and their purity is higher than SWCNTs. SWCNTs are denser than MWCNTs [16, 17]. Details are illustrated in Table S1 (Supplementary Information).

CNTs are hydrophobic thus they are insoluble in water, and it is also difficult to dissolve them in other solvents, which limits many of their applications in the industry. Various molecules of different chemical structures can be conjugated with CNTs which leads to its potential applications in the biomedical field [18–20]. CNTs are explored in drug delivery since it improves the penetration of the drug into the cells and for having a better drug action. Its use in anticancer treatments involves selective targeting which is done through surface functionalization. In tissue engineering, the improvement of the mechanoelectrical aspects of scaffolds, to permit chemical reactions to take place inside the cells and for the sensation to take place in the micro ambiance of the cell is done by the CNTs [21]. In biosensors, functionalized CNTs can cross biological barriers easily and also penetrate individual cells. The release of CNTs from cells and the mechanism of internalization attract the interest of CNTs in biosensors [22].

The major focus of the review is to present the application and manufacturing techniques of CNTs considering the economical and future advancements in the area of biomedical. Various functionalization techniques have been described in the subsequent section. Five major biomedical applications of CNTs such as drug delivery, biosensors, bioimaging, tissue engineering, and cancer treatment have been discussed and their current status is summarized. The major challenge for the application of CNTs in biomedicine is the toxicity of CNTs is discussed in-depth and its possible solution is presented. Here in the review, we have also mentioned the economics of the current market, its major manufacturers, and costs have been listed. The timeline of CNTs and their biomedical applications is shown in Fig. 1.

2 Synthesis of CNTs

The major synthesis techniques used for SWCNTs and MWCNTs are arc discharge method, laser ablation method, chemical vapor deposition (CVD) method, spray pyrolysis, and flame synthesis method.

The arc discharge is a method in which plasma is generated through the electrical breakdown of a gas. Due to high van-der-Waals' interaction, the nanotubes are formed in bundles [23, 24]. In laser ablation, an inert atmosphere is maintained and vaporization of a piece of graphite is done by laser irradiation. CNTs are formed in the form of soot which is subsequently cooled at the walls of a quartz tube [7, 25]. In chemical vapor deposition (CVD) technique, the furnace tube which contains the catalytic material is heated to a certain growth temperature after which the carbon feedstock is made available. The carbon feedstock includes hydrocarbons in the gas, liquid, and solid-state [7, 16, 26, 27]. The flame synthesis process is autothermal and provides an optimal temperature for obtaining the preferred conditions for synthesis. It involves the growth of CNTs by the introduction of a catalyst. The catalyst can be in the form of solid support or in the gas phase (floating catalyst). The flame provides energy and chemical species in the synthesis of CNTs [10, 26, 28, 29]. Spray pyrolysis is a method for forming thin films and synthesizing thin films of metals, metal oxides,

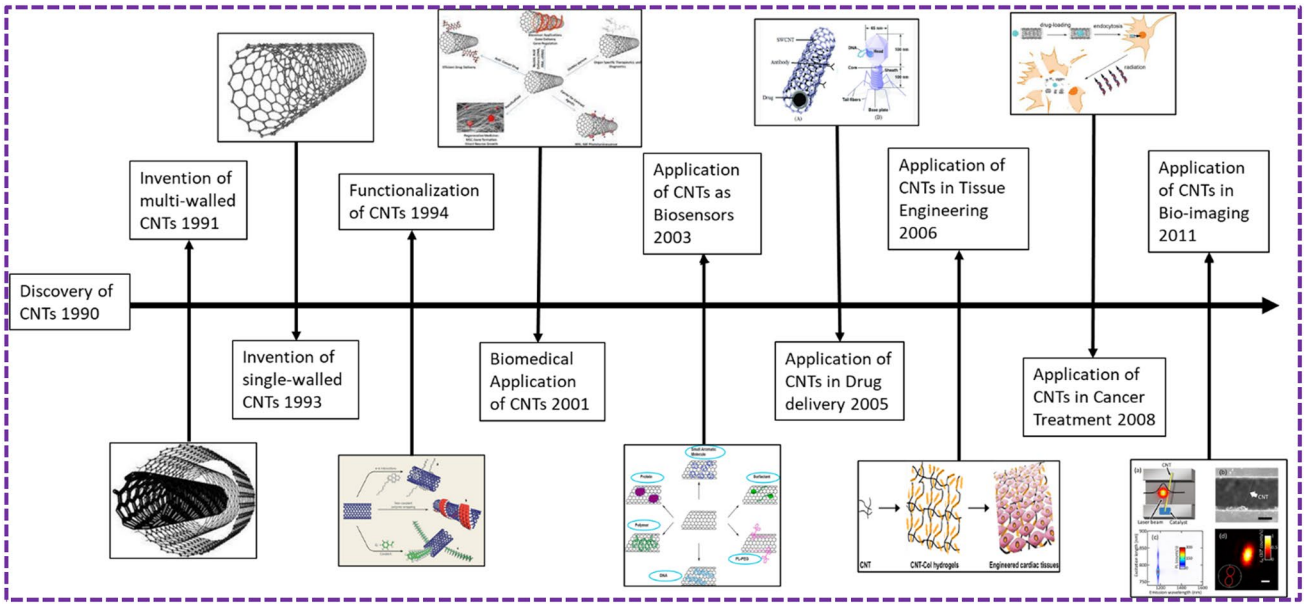

Fig. 1 The timeline of carbon nanotubes and their biomedical applications

sulfides, and nitrides. This method has an edge over others as by this method we can produce large-sized CNTs on a commercial scale [16, 30–32]. The different methods of synthesis of CNTs are summarized with their advantages and disadvantages and listed in Table S2 (Supplementary Information).

3 Functionalization of CNTs

CNTs possess few properties which restrict their direct use in biomedical applications such as limited solubility in both aqueous as well as in non-polar organic solvents, in addition, it also has a relatively short half-life of about 3–3.5 h, immunogenicity, coalescence to form thick bundles, and bio-incompatibility [33]. These are the reasons that the conjunction of CNTs with inorganic and organic molecules is hindered, which makes the functionalization of CNTs a crucial step for its application in biomedical systems. Through the functionalization of CNTs bundles are broken down which is essential for enhancing the solubility of CNTs. Functionalization not only enhances the solubility of CNTs but can profoundly affect the biocompatibility, toxicity, and surface properties of CNTs and it also creates an opportunity to load proteins, genes, or drugs to such functionalized CNTs for making an effective delivery system [20, 34]. Functionalization of CNTs can be majorly classified into three types based on their surface functionalization; covalent, non-covalent functionalization, and endohedral filling of CNTs inner space [35] depicted pictorially in Figure S1 (Supplementary Information).

In covalent functionalization, the formation of a covalent bond takes place between the functional entities and the carbon skeleton of CNTs [36]. Reactive reagents are utilized for the functionalization of CNTs with functional groups such as carboxylic, alkyl, amide, and phenyl [37]. There is a varied range of techniques of functionalization such as diazonium reactions, reductive alkylation, 1,3-dipolar cycloadditions, nitrene additions, and halogenations. But these processes require a long reaction time, a large excess of reagents, very reactive intermediates, high temperatures, and harsh reaction conditions, which affect the compatibility and stability of the functional groups. Such factors limit the possible applications of CNTs functionalization. Depending on the type of bonding reagent used, the classification of covalent functionalization is shown in Fig. S2 (Supplementary Information). A lot of research is ongoing to develop new methods which can operate under milder conditions and result in satisfactory outcomes [38]. Treatment with HNO_3 and H_2SO_4 which are strong oxidizing agents is one of the most commonly used methods for functionalization. It creates a carboxylic acid group that can further be reacted to many other different functional organic groups giving a wide variety of functionalized organic compounds. Carboxylic group when reacted with long-chain hydrocarbons it enhances the de-solubilization of CNTs in non-polar solvents. Even though covalent functionalization provides a wide range of functionalized CNTs there are also some setbacks in this process, the sidewalls of the CNTs are damaged which creates a large number of defects that may result in extreme fragmentation of CNT into smaller length nanotubes.

In non-covalent functionalization, as the name suggests there is a formation of non-covalent binding (adsorption forces) such as electrostatic force, hydrogen bonds, van der Waals force, and π-stacking interactions due to adsorption and wrapping of biomolecules, surfactant, polymers, and other chemicals [37]. Non-covalent is advantageous in comparison to chemical functionalization (covalent functionalization) as it can be operated in comparatively mild reaction conditions and the perfect graphitic structure of CNTs can be sustained by maintaining sidewalls and structural properties [39]. Based on the nature of non-covalent interactions, the classification is shown in Fig. S3 (Supplementary Information).

The endohedral filling process of functionalization CNTs is opened up at the initial stages and filled with the requisite organic or inorganic molecules. The process and selected molecules are essential to be highly sensitive while attaching the carbon pentagonal structure at the ends of the CNTs. Here, various chemical techniques are employed in endohedral filling which are highly selective while attacking the ends of the tube. Endohedral filling methods can be operated under mild conditions such as lower temperatures to fill CNTs with fullerenes and other organic molecules [40].

The aforementioned functionalization techniques have their respective advantages and disadvantages. Non-covalent functionalization and covalent functionalization are employed to amplify and improve the dispersion of CNTs in solvents and to reduce the toxicity of the CNTs. Whereas endohedral filling helps in increasing the density and strengthening the CNTs thus reducing the stress–strain transfer among the molecules. The most widely used approach for favoring the dispersion of CNTs in water, is through non-covalent functionalization (adsorption) using surfactants on the outer surface of CNTs as the hydrophobic part of it can be adsorbed on the surface and the hydrophilic part can increase the affinity towards the surrounding medium to increase CNTs dispersion [41]. To enhance the solubility of CNTs and stabilization in non-polar solvents, covalent functionalization can be done by attaching aliphatic amide function to double-walled carbon nanotubes (DWCNTs) [42].

Functionalization is one of the crucial steps when utilizing CNTs in industrial applications. It has numerous benefits such as end-cap chemistry, defect-sit repair, and biorecognition of molecules. Functionalized CNTs also play an important role in manufacturing CNTs-based modified electrodes [43]. CNTs display a great potential for application in bioengineering when they are functionalized with biological molecules such as nucleic acids, proteins, and peptides. Functionalization of CNTs with various functional groups can enhance the antimicrobial activity of CNTs as interaction or direct contact with functionalized CNTs aggregates destroys the cell membrane and induces apoptosis [36]. These benefits and characteristics which are developed in the CNTs after functionalization widen the perspective for the advancement of their properties and application in the biomedical field. Hence, functionalization is one of the potential remedies for solving the challenges that are aroused from fabrication and the interfacial properties.

4 Biomedical applications of carbon nanotubes

In this review, we have targeted five major applications of CNTs in the biomedical field as depicted in Fig. 2.

4.1 Drug delivery

Administration of drugs can be done by various methods and routes for targeted drug delivery. Various vectors are employed for drug delivery such as polymers and nanocomposites [44]. However, there are a few shortcomings in these methods of drug delivery. For example, during the use of polymer hydrogel formulation containing erythropoietin (EPO), it requires a surgical excision after the drug is administered since the polymers are not biodegradable [45]. In addition, when oral administration is done using natural polysaccharides, the rate of dissolution is very fast in the stomach due to acid attack [46]. Such issues can be sorted using CNTs instead of polymers. CNTs are biodegradable, in addition, it does not require surgical excision after the administration of the drug. Various techniques have been developed to load various biologically active moieties that can be delivered to the cell cytoplasm and nucleus [47]. CNTs chemical properties allow the introduction of various entities simultaneously on the tube such as targeting molecules, drugs, contrast agents, or reporter molecules, thus these can be used simultaneously [48]. Drugs with low water solubility, low inherent dissolution rate, and low oral bioavailability limit their therapeutic applications. Xu et al.

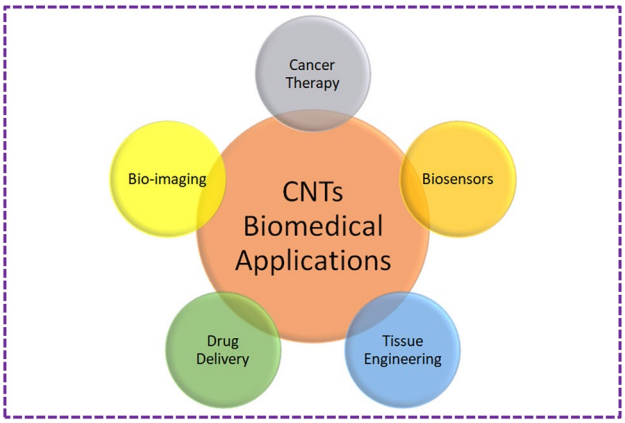

Fig. 2 Various biomedical applications of carbon nanotube

reported the electronic properties and interaction mechanisms of Efavirenz (EFV) with the CNTs using density functional theory (DFT). The adsorption of EFV on CNTs is more favorable due to the pi–pi interactions. Figure S4 (Supplementary Information) shows the strong non-covalent interactions between the CNTs-EFV pair [49]. Small molecules such as chemotherapeutic cancer drugs can be loaded on CNTs by non-covalent or covalent functionalization for cancer treatment which may pave the way towards targeted drug delivery.

Generally, cleavable bonds form the linkage between the covalently conjugated drug molecules and the functional groups that are present on the CNT's surface or with the polymer coating of the CNTs via amide bonds. Anticancer and antifungal drugs can be linked to functionalized CNTs through 1,3-dipolar cycloaddition for drug delivery. In the case of intracellular transportation of platinum(IV) complex, non-covalently PEGylated SWNTs are used in the longboat delivery system which is after the endocytosis is reduced to a cytotoxic component i.e., platinum(II) for the destruction of the cancer cells. In addition, the in vivo and in vitro drug delivery for chemotherapeutics such as cisplatin, paclitaxel, and others, are covalently conjugated to CNTs. For example, a drug delivery system developed with carboxyl chitosan and SWCNTs enhanced the cell death of human alveolar carcinoma epithelial cell lines 2.7 times in comparison with the commonly used etoposide (ETO) in an in vitro test, and the releasing mechanism of the system is determined by the pH conditions [50]. Table S3 (Supplementary Information) illustrates the recent drug delivery applications of CNTs. Karthika et al. studied the biocompatibility of TiO_2 coated gold nanoparticles decorated on MWCNTs for the targeted delivery of Doxorubicin (DOX) [51] and Karimzadeh et al. analyzed the bond properties of DOX with the carboxyl functionalized pristine SWCNTs [54]. Chen et al. have reported functionalization of the MWCNTs with *N*-methyl 4-vinyl pyridine iodide and methacrylic acid which significantly enhanced water compatibility (the concentration in water ranged from 30 to 70 mg/mL). Functionalized MWCNTs showed significant cytotoxicity toward human alveolar epithelial cells (< 10%) [52]. Mirsalari et al. performed molecular dynamic simulations to study the adsorption of an anticancer drug Dacarbazine (DAC) into the inner and outer surface of pristine and functionalized carbon nanotubes (FCNTs) with four carboxylic acid groups in an aqueous solution. Results depicted that the interaction is controlled by the pi–pi interactions with the special orientation of DAC molecule [53]. M. Yoosefian and M. Jahani functionalized SWCNTs with the carboxylic group and loaded them with droxidopa which exhibited efficient drug loading via chemisorption with an adsorption energy of − 0.714 eV. Authors reported adsorption of droxidopa on the carboxylated site of the sidewall of SWCNT via different active sites [55]. In 2017, a pH-sensitive dual drug delivery system was developed for chemotherapy with large inner diameter MWCNTs. Non-covalent functionalization with Doxorubicin and Cisplatin was achieved for anti-tumor action. Cisplatin was enclosed inside MWCNTs where folic acid, polyethylene glycol, and doxorubicin were used as the three-layered blockers. Cisplatin loading up to 84.56% was obtained with maximum anticancer activity at pH 6.5 [56]. Enormous experimental and theoretical modeling techniques are also being developed to guide the complete design process of the CNT-based drug carriers [57].

4.2 Biosensors

Cremer in 1906 demonstrated that the concentration of an acid in a liquid is proportional to the electric potential arising between fluids located on opposite sides of a glass membrane [58]. However, the first true sensors were developed by Leland C. Clark, Jr in 1956 for oxygen detection. In his honor, this electrode is called 'Clark Electrode'. Biosensors are devices which are used to detect the presence or concentration of a biological analyte, such as a microorganism, biomolecule, or biological structure. Biosensors have a thin layer that serves as a support to immobilize biomolecules with biorecognition sites. Such biomolecules may include proteins, enzymes and other macromolecules such as cell receptors and antibodies, oligo- or polynucleotides, and micro-organisms. Some of the biosensor applications may even contain whole biological tissues that exhibit specific interactions with analytes [59].

The traditional methods for diagnosis and detection of diseases are slow, laborious, expensive, invasive, and require highly specialized and sensitive instruments. Such disadvantages have been overcome by introducing biosensors with CNTs as transducers. CNTs have shown a significant increase in sensitivity, superior mechanical strength, higher electrical conductivity, serve as efficient signal transducers. Such properties make CNTs perfect nano-transducers in biosensors. Further, CNTs have good biocompatibility and outstanding chemical stability which increase the lifespan of biosensors [60]. Specifically, MWCNTs support protein immobilization while maintaining the biological activity of the proteins/enzymes [8].

A biosensor usually has three electrodes i.e., a reference, a working, and a counter electrode. The reference electrodes provide a stable, drift-free, reference voltage value. Commonly used reference electrodes are hydrogen gas electrodes, calomel electrodes, etc. The counter or auxiliary electrode provides an input potential to the working electrode and completes the circuit to allow charge flow. The working electrode is the electrode where the required electrochemical reactions happen. It should have a high reproducible response, signal-to-noise ratio, no interfering reactions over

the potential of interest, high electrical stability, easy availability, low toxicity, low cost, and prolonged life. Owing to these factors, the working electrodes are made from noble metals such as Pt, Ag, Au, or Hg and C in the form of carbon paste or graphite. Hence, glassy carbon electrodes coated with CNTs are preferred for biosensing applications [61]. The formation of biofilms is a challenge for implantable sensors. The biofilms are formed by the nonspecific binding of serum proteins which results in attenuated sensor response. To overcome such challenges, various strategies have been employed to resist protein adsorption. The strategies include coating the surface with highly hydrophilic, uncharged, and sterically hindered polymers like polyethylene glycol [62]. Sharifi and Fayazfar developed a nanocomposite sensor for doxorubicin hydrochloride detection with a modified electrode based on electrochemical growth of gold nanoparticles on the MWCNTs-COOH surface that enhanced its electrocatalytic activity, stability, and selectivity. The DOX detection range was from 10^{-11} to 10^{-4} M with the detection limit of 6.5×10^{-3} nM under optimized conditions [63]. CNTs modified biosensors have a broad range of applications as they promote electron transfer reactions [64]. It includes glucose biosensors, protein sensors, nucleic acid sensors, immunosensors, and infection sensors. A low-cost and reusable immunosensor for lung cancer was developed by Singh et al. using graphene oxide and CNTs. The immunosensor reported by Singh et al. had the highest current, stability, reproducibility, and rapid response to the analyte [65]. Cancer cell detection with biosensors leads to rapid and early detection with a higher detection limit. Figure S5a (Supplementary Information) depicts the polydopamine coated CNTs which enhanced electrochemical detection of cancer cells using folic acid targeted to-sensing strategy and Fig. S5b (Supplementary Information) shows an electrochemical DNA biosensor for detection of cancer-based on gold nanoparticles aligned CNTs [66]. Glucose biosensors are vital as testing glucose levels are important to reduce complications in the long run. They measure the glucose level and play a major role in diagnosing, controlling, and treating diabetes mellitus [21].

Biosensors find applications in point-of-care devices, continuous glucose monitoring systems, and self-monitoring of blood glucose (SMBG) devices. The goal of SMBG is to help the patient achieve and maintain average blood glucose concentrations to delay or even prevent the progression of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (stroke and coronary artery disease). Timely self-testing provides opportunities for detecting hypoglycemia and providing real-time information for adjusting medications, dietary regimens, and physical activity to achieve glycemic goals and treatment of diabetes. Regular and frequent blood glucose measurements may provide data for optimizing and changing patient treatment strategies. Glucose biosensors work due to the interaction of CNTs immobilized hexokinase or glucose oxidase (GOx) or glucose-1-dehydrogenase (GDH) with the substrate, which generates the amperometric signals.

In enzyme electrodes, there are two working parts namely the conducting part and a specific enzyme layer. The conductive part amplifies the signal of an analyte whereas the enzyme layer provides selectivity to the biosensors. Each enzyme has a biological affinity for a unique substrate molecule, enabling it to catalyze specific biochemical reactions. The response of each enzyme to a substrate might differ depending on the system. Dehydrogenases and oxidases are the most commonly used enzymes that generate H_2O_2, leading to the excitation of electrons at a certain potential which basically is the signaling mechanism of a biosensor [67]. An ultrasensitive standalone CNT aerogel has been biosensor developed by Prakash et al., for the targeted detection of nucleic acids with a limit of detection of 1 pM with a turnaround time of less than 20 min. High sensitivity was obtained due to the exhibition of linear ohmic and near isotropic electrical properties by the multi-directional tenuous network of clustered CNTs embedded into the CNT aerogel electrode [68].

Recently, biosensors have shown excellent results in the detection of viruses such as Influenza A and SARS-CoV-2. For instance, Tran et al. proposed HNO_3 functionalized CNTs on which influenza virus DNA was immobilized for detection of influenza A. Biosensor works on CNTs field-effect transistors [69]. A selective, very sensitive, and quantifiable CNT-FET-based antibody functionalized biosensor was designed and developed by Zamzami et al. for SARS-CoV-2 S1 antigen detection in the buffer solution. The surface modification of CNTs in biosensors was done using PBASE linker molecules, and anti-SARS-CoV-2 S1 was immobilized on the PBASE layer. Antigen-specific concentration-dependent sensing response over a broad range of concentrations (0.1–5000 pg/mL). Thus, the developed biosensor is simple, inexpensive, easy to use, versatile, and can be a prototype for SARS-CoV-2 S1 antigen detection and diagnosis of SARS-CoV-2 infection [70]. Table S4 (Supplementary Information) reports some of the recent applications of CNTs in the field of biosensors.

Reza et al. utilized multiple enzyme immobilization strategies for the fabrication of MWCNTs-Indium Tin oxide (ITO)-enzymes biosensors for urea detection. Enzymes Urease and glutamate dehydrogenase are attached to MWCNT/ITO electrode surface covalently using ethyl-dimethyl aminopropyl-carbodiimide and N-hydroxy-succinimide spacers. Broad detection range (0.83–24.9 mM), low detection limit (1.3 mM), and higher sensitivity were observed due to excellent electrochemical properties of MWCNTs and covalent functionalization of dual enzyme improved biosensor stability and sensitivity [71]. For the early detection of multidrug

resistance (MDR), Zhang et al. explored a new strategy by CNTs–drug supramolecular interaction electrochemical sensor. Here, different ratios of the sensitive leukemia cells K562 and its MDR variants K562/A02 were applied for MDR simulation. The cathodic peak current showed a good linear response to the fraction of MDR with a correlation coefficient of 0.995 was observed for the cathodic peak current indicating an easy prediction of the MDR fraction based on the calibration curve of the cathodic peak current versus the fraction of MDR [72]. A sensor-based on polyfluorene-g-poly(ethylene glycol) (PF-g-PEG) and MWCNTs was developed for the quantification of ethanol in alcoholic drinks by Bekmezci et al., with high sensitivity [73]. Ghrera et al. fabricated an impedimetric microfluidic-based biosensor for quantification of the DNA sequence specific to chronic myelogenous leukemia (CML). The MWCNTs modified by immobilization of CML specific deoxyribonucleic acid probe along with sealing of the biochip by a poly(dimethylsiloxane) microchannel for fluid control was reported. Under optimal conditions, such a microfluidic biochip exhibited a good calibration range from 1 μM to 1 FM and a response time of 60 s [74]. Savalia et al. analyzed the brucine in the biological environment with the glassy carbon electrode modified with SWCNTs and Nafion composite film for the first time. Authors reported dynamic linear range from 1 nM to 8 μM with a high sensitivity of 340.8 μA μM^{-1} and a limit of detection corresponding to 0.11 nM was achieved under optimized conditions [75].

4.3 Bio-imaging

Numerous desirable properties of CNTs are ideal for optical detection. The transitions in CNTs occur in the near-infrared region (NIR) of the electromagnetic spectrum result in minimal interference in the signal. The infrared spectrum between 900 and 1300 nm is an optical window which is of tremendous importance in biomedical applications due to the lower photo-absorption and small auto-fluorescent background. In the selected band of the spectrum, the absorption is lower, enabling greater penetration depth for optical signals. In addition, CNTs also possess excellent photostability [76]. Raman scattering and fluorescent spectroscopy are the techniques available for tracing the path of CNTs in the body for a longer duration of time. The CNTs are retained in the cells for repeated cell divisions due to their hydrophobic nature, indicating that they can be used for designing probes for studying stem-cell differentiation and proliferation. CNTs are potential imaging contrast agents in optical detection, magnetic resonance, Raman scattering, photoacoustic, fluorescent video imaging, and nuclear imaging techniques [77]. Welsher et al. used SWNTs as NIR-II (1100–1400 nm) contrast agents to perform the high frame rate fluorescent video imaging of mice i.v. injected with SWNTs and investigated the path of SWNTs through mouse anatomy. By applying principal component analysis (PCA), the anatomic resolution of organs was greatly enhanced. Here the pancreas can be distinguished after PCA analysis of NIR-II fluorescence images. The authors illustrated that the NIR-II fluorescence imaging, together with PCA, can provide a powerful tool for a broad range of potential applications from biomedical research to disease diagnosis [78].

The visualization of fluorescent dyes or proteins as labels for molecular processes or structures is called fluorescence imaging [79]. A wide range of experimental observations including the location and dynamics of protein expression, molecular interactions, and gene expression in cells and tissues are reported [80]. For monitoring the fluorescent signals in tumors and other organs the technique of high fluorescent rate imaging and principal component analysis (PCA) are used. It was observed that in the tumors the fluorescent signals were found after the 20 s of being injected and remained for up to 72 h [81]. In magnetic resonance imaging (MRI), imaging of the whole body takes place without any depth limit. Hence, MRI is clinically more relevant in comparison to other diagnostic techniques. Functionalized CNTs are found to be easily detectable by various techniques [82]. Functionalization is performed by attaching a heavy atom (e.g.: gadolinium) to the surface of the fullerene or caging it inside the CNTs [83]. Such heavy metals which are attached to CNTs serve as X-ray contrast agents [84]. CNTs can provide enhancement of images for various modalities and can be used as NIR fluorescent labels, radiolabels, and MRI contrast agents. Raman bioimaging is a process in which photons are emitted under light excitation with shifted wavelengths. The stronger resonance in Raman scattering by SWCNTs is of paramount importance in bioimaging and sensing applications [85, 86]. Information about the microenvironment of the cell can be obtained using Raman spectroscopy as it is sensitive to functional groups in a molecule. Hence, the introduction of additional probes subsequently increases the sophistication [87]. Photoacoustic (PA) imaging detects sound instead of light. Since the CNTs have strong NIR absorbance, they can also act as photothermal agents. In photoacoustic imaging, laser pulses are absorbed by light-absorbing molecules to produce heat in the biological sample, which induces transient thermoelastic expansion which leads to wideband ultrasonic emission. The light-absorbing molecules can be contrast agents or endogenous molecules. 2D and 3D images can be constructed by the ultrasonic microphone which can detect the ultrasonic emissions [77]. Figure S6 (Supplementary Information) shows NIR-II fluorescence imaging of PEGylated SWCNTs inside a live mouse.

It was observed that CNTs reached the lungs first, followed by the kidneys, liver, and spleen. The anatomic resolution of the organs was substantially improved by

principal component analysis (PCA) [77]. In vivo PA imaging, Gambhir et al. for the first time adopted Arg-Gly-Asp (RGD) peptide conjugated SWNTs as PA contrast agents. In the SWCNT-RGD injected group, strong PA signals could be observed from the tumor, whereas in the SWCNTs injected groups, only weak signals were observed [88]. In another example to detect, map, and quantify the trace amount of SWCNTs in historical tissue specimens, Avi et al. adopted photoacoustic microscopy. Noise equivalent detection limit of about 7 picograms was achieved [89]. In nuclear imaging, radioisotopes can be introduced as an external label. It improves the versatility of CNT-based imaging probes. SWCNTs which are radiolabeled have high sensitivity and have no tissue penetration depth limitation which makes them excellent for use in nuclear imaging [90].

A few excellent breakthroughs in the field of bioimaging are listed in Table 1. Yudasaka et al. reported that CNTs coated with poly(2-methacryloyloxyethyl phosphorylcholine-co-*n*-butyl methacrylate) (PMB) which is an amphiphilic and biocompatible polymer resulting in high-quality images of brown fat. Brown fat is a heat-productive adipose tissue that is becoming an obesity-associated metabolic disorder therapeutic target. PMB-CNTs provide clearer and brighter images as compared to the organic dyes used due to the high level of transmitted light passing through the body with less light scattering [91]. SWCNTs conjugated with cyclic Arg-GlyAsp (RGD) peptides were used for the detection of a tumor using photoacoustic imaging. These conjugated SWCNTs provided high-resolution images along with a substantial depth of penetration [92]. Delogu et al. found that MWCNTs are highly echogenic in the liver and heart by examining this on a pig. The ultrasound signal off-MWCNTs observed was higher than the pristine MWCNTs, graphene oxide, and functionalized SWCNTs (f-SWCNTs). The use of CNTs as ultrasound contrast agents has very wide scope in the bioimaging field [93]. Mathew et al. have reviewed the use of graphene quantum dots for the imaging of osteosarcoma [94]. Liu et al. identified the first multiplexed Raman imaging of live cells using three types of SWCNTs with different ^{13}C doping ratios so that the corresponding cell lines can be recognized by Raman bioimaging [86].

4.4 Tissue engineering

Tissue engineering is a rapidly growing interdisciplinary branch of science that combines medicine, bioengineering, material sciences, pharmaceutical sciences, and life sciences. The main motive is to replace diseased or damaged tissue with biological substitutes which can be restored and maintain normal functioning. In tissue engineering, the patient's cells or tissues are used in such a way that the normal functionality of the damaged tissues or organs is restored. Tissue engineering help in decreasing the risks involved in transplants from donors [95].

In tissue engineering, the 3D scaffold is used which maintains the mechanical integrity, elasticity, and cell-specific biochemical environment of the tissues. A scaffold is said to be perfect when it contains a unique spatial distribution within the microenvironment to continuously provide nutrients and growth factors to the growing cell. Scaffolding materials are characterized into three types based on their origin as natural materials, synthetic polymers, and inorganic materials. Natural materials include biopolymers with high strength such as collagen, fibrin, and chitosan. Natural materials have better biocompatibility and can undergo biodegradation. Synthetic polymers which are highly flexible and have unique physicochemical properties, are used for 3D scaffolding and include resorbable products such as polyesters, polylactides, and polyurethanes which are approved by the FDA [96, 97]. Certain inorganic materials are used in bone tissue engineering, such as calcium phosphate cement and ceramics, bio-ceramics and bioactive glass, etc. but brittleness and inflexibility remain a major concern [98, 99].

In tissue engineering, the cell mass needs a suitable extracellular matrix (ECM) for proper growth. The ECM is a 3-D network of the macromolecules and other essential building blocks of life which mostly includes collagen, glycoproteins, hydroxyapatite, minerals, and enzymes. These molecules give structural and biochemical support to the growing cells. The composition of ECM may vary from organism to organism but the basic functions are the same i.e., cell adhesion,

Table 1 Application of CNTs in bioimaging

Type of CNT	Functionalization	Application	References
SWCNTs	Poly(2-methacryloyloxyethyl phosphorylcholine-co–n-butyl methacrylate; PMB)	Imaging of brown fat	[91]
SWCNTs	Cyclic Arg-GlyAsp (RGD) peptides	Tumor detection	[92]
MWCNTs	–	Ultrasound scan of liver and heart	[93]
SWCNTs	Graphene quantum dots	Imaging of human osteosarcoma	[94]
SWCNTs/MWCNTs	–	Raman Bio-imaging for live cell imaging	[86]

intercellular communication, and cell nourishment. Balancing ECM around the growing cells assists in triggering a specific cellular response by the initiation of critical biochemical and biomechanical signaling. This response stimulates the generation of functional cells and their homeostasis [100]. Mimicking the ECM is a great challenge due to its complex architecture and composition. CNTs-based scaffolds show excellent similarity to the microenvironment of the ECM, they have been established in tissue engineering as an innovative tool.

CNT-based 3D scaffolds have exceptional mechanical properties along with high tensile strength and elastic moduli, making them better for use in composite scaffolds [101]. Shape, size, roughness, and surface area of CNT-based 3D scaffolds are almost the same as that of collagen fibers which are embedded in the cell ECM. It provides a 3D network that supports and guides cell differentiation, communication, and proliferation. CNTs can interact and adsorb the extracellular proteins which enhances cell interaction and scaffold biocompatibility [102]. Cell scaffold interactions can be improved by modifying the CNT surface or functionalization of their surface area which also helps in cell spreading. Amiryaghoubi et al. combined CNTs and graphene oxide (GO) with natural and synthetic polymers with the required characteristics which makes them perfect to serve as multifunctional materials in bone and cartilage tissue engineering which can regulate the osteogenic and cartilaginous abilities of stem cells [103]. Specific modifications can be done with alcoholic or carboxylic groups to the walls or the end of the nanotube [104]. The scaffold design and cell differentiation are improved as the CNTs have unique thermal and conducting properties [105]. It offers better cell support which is crucial for angiogenesis and vascularization while still allowing scaffold degradation. Gorain et al. reported exceptional improvement in electrical stimulation and electrical conductivity in cardiomyocytes on the inclusion of SWCNTs or MWCNTs into polymeric, elastomeric, and fibrous scaffolds [106]. CNTs provide the preliminary structural reinforcement which is needed for daughter tissue scaffolds. Ding et al. treated cardiovascular diseases with altered SWCNTs in the form of tissue-engineered blood vessels (TEBV). To reduce the loss of drugs caused by blood flow, SWCNTs are used to build an irregular mesh to coat TEBV [107]. CNTs are non-biodegradable; however, it can be rapidly removed from the body [108]. CNTs incorporated scaffolds improve cell adhesion, reduce degradation rate, and enhance mechanical properties, morphogenesis, and cell signaling. CNTs also exhibit periodic release of growth factors and nutrients at a controlled rate for the progress of cell division and development of functionalized tissues [109]. It is proven that MWCNTs are more effective than SWCNTs as the MWCNTs possess lower defects, straighter, and have less tendency to distribute. Figure S7 (Supplementary Information) shows schematically how CNTS and composite materials are used for 3D scaffolding. It demonstrates the applicability of apatite mineralization for promoting new bone formation [110]. Recent noticeable advances in the tissue field are listed in Table S5 (Supplementary Information).

Wang et al. found that the mechanical property of 100% MWCNTs monolith was close to that of human bone [111]. Perdana et al. explored functionalized multiwalled carbon nanotubes with the carboxylic groups and an anodic procedure was used to obtain TiO_2 nanotubes. Studies found that carboxylic group and hydroxyapatite enhanced the mechanical and bio-properties of the material. The new complex coating has surface energy higher than 30 mN/m which indicated to have a better biological adhesion and osteoblast nature [112]. Yan et al. reported that SWCNTs accelerate maize seminal root growth. In further trials of gene transcription analysis, it was observed that SWCNTs could increase the expression of seminal root-associated genes and decrease root hair-associated gene expression [113]. Gerasimenko et al. notified in their work that polymeric matrix reinforced with CNTs can be used as a structural material for bone cement as well in skin tissue engineering. Polyurethane and CNTs-containing composite with excellent electrical and mechanical properties can be utilized for stimulation of growth of bone and nervous tissues [18]. In work done by Xia et al., CNTs are non-covalently functionalized by hyperbranched polyglycerol sulfate (APG) via sonication, and the stability and biocompatibility of hPGS-dispersed CNTs were compared with commercial dispersants. The nanostructured fibrous scaffolds are prepared by coating hPGS-dispersed CNTs onto the electrospun polycaprolactone (PCL) fiber substrates to achieve PCL-CNT-hPGS. Such fibrous scaffolds can serve as a biocompatible platform for promoting adhesion and proliferation of induced pluripotent stem (IPS) cells [114].

4.5 Cancer treatment

Cancer comprises a group of diseases in which uncontrolled cell growth occurs. These cells have the potential to expand to other organs or body parts. These cancerous cells lead to the suppression of healthy cells leading to improper functioning of the infected tissues/organs. It may occur due to exposure to ionizing radiations, multiple genetic alterations, or ingestion of carcinogenic substances [115]. Numerous studies have been conducted to design new strategies and methodologies for effective cancer treatment but we still lack a super effective cure. The current treatment methods include radiotherapy, surgical interventions, chemotherapy, and immunotherapy. Such techniques have severe side effects associated with them. Hence, nanomaterials-based systems are being considered a promising approach toward optimizing the success rate of cancer therapy, which includes

target-specific drug delivery, diagnosis, and imaging. Currently, nanomaterials being tested for these specific applications are carbon nanotubes [116], gold and silver nanoparticles [117], liposomes [118], etc. For example, an analytical device for sensing an anticancer drug in the entire blood was developed by Zhou et al., using methotrexate (MTX) as the detection model system. MTX is employed for numerous cancer treatments; however, severe side effects can be caused by excessive use of this medicine; hence regulating the MTX concentration in the blood becomes essential to create an optimized dosage for patients and reduce the chances of intoxication [119].

Properties of CNTs such as large surface area, conjugation and encapsulation ability, target-specific action, higher drug loading capacity, and strong near-infrared (NIR) radiation absorbance make them viable for use as a mediator in chemotherapy and photothermal therapy [120]. CNTs can also adsorb pathogenic micro-organisms and conduct heat. In addition, CNTs can cross the cell membrane and penetrate tumor cells due to enhanced permeation, and retention effects, and owing to their needle-like shape [121]. In surface functionalization of CNTs, the attachment of molecules may be through covalent or non-covalent bonding. Target specificity can be achieved by particular type of functionalization. Acid-treated CNTs develop a –COOH group on the surface which can be further modified by attaching carbohydrates, amines, thiols, antibodies, and glycoproteins to achieve target specificity [122]. Functionalization improves biocompatibility, dispensability, solubility as well as aid in reducing the CNTs agglomeration, and also helps in rapid endocytosis. All such properties improve the effectiveness, rapidity, and selectivity of cancer therapy and diagnosis [123]. It has been observed that a higher anti-tumor effect can be attained using SWCNT-PTX than the generally used clinical Taxol used in a murine 4T1 breast cancer model, because of prolonged blood circulation times and the enhanced permeability and retention (EPR) effect leading to a higher accumulation in the tumor [124]. Various mechanism for inducing the cytotoxicity of macrophages against cancer cells utilizing CNT triggering a cascade of cellular and molecular processes such as ROS generation and lysosome damage has been shown in Fig. S8 (Supplementary Information) [125]. Noticeable studies on cancer treatment are listed in Table S6 (Supplementary Information).

In the studies reported by Ahmed et al., the SWCNTs–TiO_2/Ag and MWCNTs–TiO_2/Ag conjugates were used in breast cancer treatment which exhibited minimal cytotoxicity. The conjugates formed and administered are highly selective in killing the tumor cells (effectivity ~ 60 to 40%) [126]. Oskoueian et al. found that the functionalized SWCNT linked with tamoxifen enhanced the cytotoxic action of tamoxifen up to 2.3 times against breast cancer cells and improved the therapeutic effects and anticancer potential [127]. Chen et al. reported that functionalized SWCNTs can be used as a biocompatible carrier for drug delivery in a specially designed for cancer treatment. Biotin and spacer attached to CNTs act as a tumor-recognition module showing high potency and cytotoxicity towards specific cancer cell lines [128]. Heister et al. presented a study on a triple functionalization of oxidized SWCNTs with the anticancer drug doxorubicin, a monoclonal antibody, and a fluorescent marker at non-competing binding sites. SWCNTs were shown to have a very high penetrating capability through mammalian cell membranes which allowed very high loading of drugs and also assisted the targeting of therapeutic agents to the desired site of action by conjugation to antibodies or ligands of cancer cell surface receptors, which increased the effectiveness of the treatment and reduced side effects [129]. A pH-triggered targeted drug delivery system was developed by Zhang et al. using SWCNTs as the carrier for the administration of anticancer drug doxorubicin (DOX). The drug was bound at physiological pH of 7.4 and was released at lower acidic pH. CNTs utilization has overall increased the loading efficiency and realizing rate of the drug [130].

5 Toxicity of CNTs

The type and length of CNTs, metal impurities present, the presence of solubilizing agents, and the mode of functionalization influence the toxic effects of CNTs. The high surface area to size ratio is the major reason behind the toxicity of CNTs. Increased surface area indicates more contact with the cellular membrane and also the greater absorption, adsorption, and transportation of toxins. The synthesis of CNTs itself requires intrinsically toxic metal catalysts such as ferrocene. The toxicity can also be attributed to the formation of superoxides and reactive oxygen species (ROS). Oxidative stress, membrane damage, and genotoxicity are the main mechanisms involved in CNTs toxicity [21]. Diameter dependence of toxicity of MWCNTs to the endothelial cells and the autophagy-ER stress studies on the cell counting kit (CCK-8) assay concluded that as the diameters of MWCNTs increase, there is a gradual decrease in cytotoxicity, keeping the same mass concentration [131]. CNTs can easily penetrate through the cellular lipid bilayer membrane inducing oxidative stress and causing inflammation. CNTs generate free radicals which may be responsible for cellular toxicity because of excess radicals which can oxidize DNA, proteins, and lipids in the cells. The free radicals are known activators of transcription factors and activator protein-1, which cause an inflammatory response [132]. Since CNTs are not easily eliminated from the body, hence their accumulation in the body is a more severe threat. Due to oxidative stress, ROS are formed in the cells. Increased levels of these ROS may

result in apoptosis, damage to genetic material, amino-acid oxidation, and enzyme inactivation. CNTs are taken to the spleen, kidney, and lungs for activity reduction and removal, resulting in more accumulation in such organs [133]. The acute toxicological studies revealed that within some limit, the toxicity was very less although histopathological damage was observed and proteomics analysis indicated the increased expression of proteins having antioxidant and detoxifying properties in the liver tissues [134]. Immune systems sense CNTs accumulation as pathogen invasion, and in response, macrophages phagocytize them and internalize them in phagolysosomes. However, the fibrous shape of CNTs pierces the phagolysosome membrane. Hence, CNTs can be found freely dispersed in the cytoplasm, interfering in the biochemical pathways [135]. The high physical strength of CNTs results in rupture and slicing of various delicate membranes and cell organelles causing inflammatory reactions and even tissue disruption [136]. The nanometric size and structure of CNTs enable them to penetrate brain cells. In addition, for drug delivery purposes, CNTs are generally functionalized. Hence, they can even bypass the blood–brain barriers, which release various mediators and chemicals resulting in the neuroinflammatory response [137].

6 Computational study of biocompatibility of CNTs

Before employing CNTs in biomedical applications, one must understand the biocompatibility of the CNTs and their nanocomposites which are essential to ensure the minimum hazards and toxicity. In the biocompatibility analysis, the focus is on the interaction of nanomaterials and subsequent responses from living systems. In terms of numerous thermodynamic and physical parameters, we can compare the relative biocompatibility. It can be investigated through in vivo and/or in vitro techniques. Simulation studies are being done to make the experiments more effective. Molecular dynamics simulation can be useful in analyzing the interactions of various structures at the nanoscale level with biological macromolecules. Certain experiments are not feasible to carry out in living systems and in such scenarios, the researchers resort to computational methods using a variety of sophisticated simulations software packages available such as Schrodinger simulation software, NAMD software, NBO 3.1 software, AFM, fluorometric microculture cytotoxicity assay (FMCA) for the detection and interaction of CNTs, GROMACS-3.3.3 software package, and Materials Studio 4.1 [138–141]. Simulation results help us to predict the solubility parameters, the radius of gyration, diffusion coefficient, a drug to polymer ratio, end to end distance, and the appropriate number of polymers that have the best results [142]. Molecular interactions are often related to the interaction energies which in turn decide the Gibbs free energy of the incorporation of CNTs in the intercellular cavities. Interaction energies account mainly for electrostatic and van der Waals (vdW). Molecular interactions are essential for cell adhesion specifically in tissue engineering applications. Hydrogen bonds play a vital role in the solubility of CNTs. Functionalization and composite formation with polymers increase the hydrogen bonding sites. Hydrogels help to enhance the hydrophilicity of CNTs. As the number of hydrogen bonds increases, the solubility increases which is essential for the interaction of CNTs with other drugs or polymers. Functionalized CNTs have surface characteristics and possible interactions tuned in a way to reduce the free energy and dispersion of the drug being targeted in drug delivery systems [143]. As discussed in the literature by Kamath et al. where three different polymer–drug interactions were investigated with help of MD simulations at the different drug to polymer ratios, it was found that 15 polymer chains showed the best results for DOX-loaded drug carriers based on solubility parameter results [144].

Polymer–CNTs interaction is a crucial parameter for the stability of the composite form. The uniform distribution of drugs in a polymer matrix is signified by the larger radii of gyration, enabling the stable and better encapsulation of drug molecules. The radius of gyration (Rg) is an important parameter in the screening of the polymers being used as composite materials. The reported Rg values for the poly-*N*-isopropyl acrylamide (PNIPAM), polyethylene glycol (PEG), and polyvinyl pyrrolidone (PVP) are 17.42 Å, 22.19 Å, and 15.68 Å, respectively [144]. Overall, PEG is most suitable for drug delivery applications. Computational methods based on quantum mechanical models and the Monte Carlo simulation technique allow numerical prediction of solvation free energies. One such inquisition, considering three possible interactions of CNTs with the corresponding zwitterionic species of Carnosine, revealed that on functionalization with Carnosine, the solubility of CNTs increased significantly [145]. A slightly different approach was reported by Yan et al., by forming macrostructures of CNTs such as CNT fibers and systematic evaluation of biocompatibility and immune-compatibility profiles. The toxicity to the cell lines, blood, immunologic, organ, and organ systems was quantified. No cytotoxicity to primary cell lines of the immune system was observed accompanied by no hemotoxic and immunologic response [146].

Surface morphology, types of bonds, elements, and phase content present in CNTs-based composites disclose the possible reactions on the cell lines. A plethora of analytical techniques such as scanning electron microscopy, FTIR spectroscopy, Raman spectroscopy, XRD techniques, and EDX mapping analysis can be done before the injection of composites. Working on similar lines, the carbon nanofillers hydroxyapatite (HAP) biocomposite exhibited

negligible cytotoxicity towards the Madin–Darby Canine Kidney (MDCK) cell line ever after 5 days of the incubation period. Moreover, excellent biocompatibility and nanomechanical properties were observed in the case of 2 wt% of GCNTs reinforced HAP which might be incorporated in tissue engineering [147]. In another study, carried out on mature Moscow breed roosters by implanting 0.5 mL of protein-carbon nanotube dispersion intramuscularly to the lateral shin. After 90 days of implantation, the reduction in composite volume and a greater number of connective tissue interlayers at the implantation site were observed, implying excellent tissue regeneration with mild inflammatory action of the avian immune system [148]. Compatibility studies prioritize diminishing after-effects of nanotubes on the host in which they are being injected. Recent pandemic situations compelled people around the world to investigate different angles of currently available technologies which lead to the MD and molecular docking simulation studies on binding potentials of CNTs and nano fullerenes towards various portions of the SARS-CoV-2 virus. CNTs exhibits excellent binding energies of − 26.7, − 19.7, − 15.8, − 21.1, and − 20.7 kcal/mol towards spike glycoprotein, RNA dependent RNA polymerase, main protease, papain-like protease, and RNA binding domain of nucleocapsid protein, respectively. The pathogenic mechanism of the virus might be inhibited by these interactions [149]. Compatibility study can be extended to biomedical applications such as biosensors in which electronic behavior is used for an electronic application. It is detected by observing changes in conduction across the channel. MD simulation showed promising results in detecting these changes [150]. In Fig. S9A, B, the effects of hydrogen bonding and hydrophobic effect with three SWCNTs 600, gamma cyclodextrin-150, and water at different time instances are shown [151].

Computational studies with various simulation techniques have made many impossible laborious tasks simple, quick, and economical. It is helpful in many aspects of the biomedical application of CNTs and it has assisted in discovering many new applications in this field in the recent decade. It will set up a background for new findings and applications in the field of biomedical and material sciences. Table 2 enlists some of the simulation studies on the drug delivery and cancer treatment applications of CNTs. For cancer treatment, the Lomustine/SWCNT system was found to be stable by Cao et al. based on the adsorption energy obtained via computational studies. The L2 conformer had larger hydrogen bonding energy and ρ values by QTAIM analysis. The density functional theory (DFT) was used and the calculations were done by the Gaussian 16 program [152]. In the compatibility simulations, Yoosefian et al. used Gaussian 09 series technique for Ifosfamide, an anticancer drug [153]. In the computer simulation study reported by Ketabi et al., carnosine and CNTs were analyzed using Quantum Mechanics (QM) and Monte Carlo (MC) simulation. The carnosine zwitterion via NH + 3-CNT was found to have the highest interaction energy. Solvation of carnosine (NH + 3)-CNT complex in water was larger than the other. Carnosine (NH3)-CNT complex had the larger complexation free energy and thus was the most stable compound in water. The solubility of CNTs in biological fluids was improved notably on functionalization with carnosine dipeptide which resulted in improving their biocompatibility [154]. In the case of drug delivery application, interactions between fullerene C24 and ephedrine (EPH), have been studied by Tomic et al. using density functional theory (DFT). DFT calculations and MD simulations have been performed with Jaguar and Desmond programs. The density of system C24 + EPH and interactivity between C24 and EPH molecules are substantially reduced with increasing temperature. MD results are particularly important for practical applications as they indicate that the release of EPH by C24 might be controlled by temperature [155]. Low biocompatibility and poor dissolution rate have limited the therapeutic effect of various antiviral medications. However, with recent advances, it has been found that nanostructures and particles can overcome these limitations. In a current study done by Xu et al., the compatibility of the boron nitride nanotubes (BNNTs) and carbon nanotubes (CNTs) as a drug delivery carrier of Efavirenz (EFV) was studied respectively. Due to abundant negative charges and aromaticity of the CNTs, the π–π stack interaction and the electrostatic interaction of EFV on CNTs are larger than that on the BNNTs, which explains the stronger interaction of EFV on the CNTs. The properties of CNTs do not change much while delivering the drug into the cells. CNTs can thus serve as a better drug delivery vehicle for the transportation of the antiretroviral EFV drug within the biological system [49].

7 Economics

The most important parameter after the type of CNTs and their properties is the cost of production. Presently developed technologies are cheaper and more efficient as compared to earlier but there is a lot more scope for innovations that would exponentially decrease the price of CNTs which would make them utilize in a lot more things than we are presently using. In recent few decades, the market of CNTs shot up extremely as they are being utilized in many biomedical applications as well as membrane technology. Currently, Asia and Europe are the hubs of CNT production among which the Asia Pacific dominates. The global market of CNT in the year 2019 was $ 670.6 million with a compound annual growth rate (CAGR) of 33.4% from 2014 to 2019. The predicted rate of growth of the CNT market is between 11.53 and 33.4%. Some global manufacturers

Table 2 Compatibility studies of CNTs for various biomedical applications

Technique used	Highlights/results	Biomedical application	References
Density function theory (DFT) The calculations were carried out by the Gaussian 16 program	QTAIM analysis was used and the L2 conformer was found to have larger hydrogen bonding energy and ρ values. The Lomustine/SWCNT system was deemed to be stable from the value of adsorption energy obtained	Cancer treatment and drug delivery	[152]
Gaussian 09 series	Chemisorption has been done to absorb the drug on SWNTs. Results have shown that the suitable SWCNT for the encapsulation of IFO has a diameter of about 13.456 Å	Ifosfamide anticancer drug	[153]
Quantum mechanics (QM) and Monte Carlo (MC) simulation	The carnosine zwitterion via NH + 3-CNT was found to have the highest interaction energy Solvation of carnosine (NH + 3)-CNT complex in water was larger than the other Carnosine (NH3)-CNT complex had the larger complexation free energy and thus was the most stable compound in water. The solubility of CNT in biological fluids was improved notably on functionalization with carnosine dipeptide and so to improve their biocompatibility	Drug delivery	[154]
DFT calculations and MD simulations have been performed with Jaguar and Desmond programs	The density of system C24 + EPH and interactivity between C24 and EPH molecules are substantially reduced with increasing temperature. MD results are particularly important for practical applications as they indicate that the release of EPH by C24 might be controlled by temperature	Drug delivery	[155]
DFT methods with the Perdew–Burke–Ernzerhof (PBE) functional	Due to the abundance of negative charges and the aromatic of the CNTs, the π–π stack interaction and the electrostatic interaction of EFV on CNTs are large than that on the BNNTs, which explains the stronger interaction of EFV on the CNTs The properties of CNTs do not change much while delivering the drug into the cells CNTs can thus serve as a better drug delivery vehicle for the transportation of the antiretroviral EFV drug within the biological system	Drug delivery	[49]

of CNT include Ultra Nanotech Private Limited, UP Catalyst, Cheap Tubes, etc. Companies produce various types of CNTs with different functional groups and properties according to demands and their application.

With the increasing demand for CNTs, new manufacturing units are being set up in China, Russia, and India. Such units would be producing CNTs at lower costs which will increase the competitiveness in the market. It would comply with other companies as well in the market to manufacture at cheaper rates and even more such units would be brought into functioning which will help reduce the cost of CNTs to such an extent that CNTs can be a trend and utilized in our day-to-day applications. Various companies are emerging worldwide in manufacturing CNTs through various techniques having functionalized properties and supplying on a commercial scale. Table S7 (Supplementary Information) lists various companies manufacturing the CNTs worldwide with or without functionalizations. Recent advances in technology lead to automated CNTs manufacturing facilities and the quality of the product is maintained using high-performance AI systems. The cost of CNTs increases as the purity of the CNTs goes higher. Several companies also provide the material characterization details of the produced CNTs such as XRD, XPS, FTIR, TEM, and SEM. This also makes it easier for the researchers to validate their findings and have better comprehensive data.

8 Future aspects

In the current scenario, there is a higher demand for action-specific drugs, personalized drugs, care services, and sophisticated treatment techniques. CNTs-based applications can be seen as an excellent alternative as they have various characteristic features. However, the problem arises in manufacturing them at an effective cost and producing non-defective CNTs. Thus, further work can be done to develop new manufacturing methods which are cost-effective and produce proper CNTs that are non-defective thereby reducing wastage. Even though CNTs have exceptional properties due to their toxic effects, their biomedical trials are still on hold. Reducing toxicity is a major research area in CNT applications in the bioscience field. CNTs are hydrophobic which inherently increases their retention time in the body leading to accumulation. In higher quantities, this might be lethal as the CNTs can bypass most of the barriers and membranes due to their small size and high tensile strength. The possible solutions may come up based on the suitable surface functionalization as well as nanocomposite formation with non-biodegradable agents like biocompatible hydrogels. Hydrogels in a way limit the dispersibility of CNTs in an organism and at the same time reduce the risk of direct exposure. Trials have been done on animals but human testing is yet to be fully explored which is resulting in the restrictions in CNTs applications generally for diagnostic and other purposes. Currently, CNTs are utilized mostly in cancer and arthrological treatments. Wide scope for CNTs in other medical treatments which are yet to be developed and can become a major part of the biomedical application in the coming decades. Till now, many researchers have suggested miscellaneous techniques for the possible use of CNTs in the biomedical field but extending CNTs-based applications from laboratory scale to industrial scale is still one of the major challenges encountered in commercializing them in the market. Considering the current challenges in the development of biomedical instruments using CNTs, our recommendations for future work are as follows.

(1) The excitement of the utilization of nanomaterials such as CNTs in the biomedical field is due to the results published in high-end journals and magazines. Various reports on overcoming the problems of toxicity, solubility, etc. are published in huge numbers every year. Along with a major focus on the scientific community in contributing to the field of biomedical research, concerns over the reliability and reproducibility of scientific data are growing every day [156–158]. Systematic efforts and methodologies must be devised to tackle such issues.
(2) Professor David Sholl and his group have extensively published on the reproducibility issues in chemical engineering [159, 160]. The authors have provided some key points to make the scientific work more reliable such as (a) triplicating the experiments and providing error bars for the data represented. (b) Extensive supporting or supplementary information must be provided so as it aids the scientific community to validate the results and reproduce the same while working on similar lines. (c) The protocols used for the synthesis of the materials and characterization techniques must be presented in a step-wise and detailed manner which can be useful for future work by any other independent researcher or research group. (d) Computational studies reported in any scientific journal must specify the details of software and version used. If the computational work is done using programming code or software which is developed in the house, it must be made available via open source or licensed copy for validation by peers.
(3) Standards must be developed to characterize the nanomaterials used in biomedical research. Benchmarking must be done to determine the quality, purity, and characteristics of pristine and functionalized CNTs which are to be used for many biomedical applications.
(4) Extensive studies must be carried out to understand more about the biosafety of CNTs. Potential risks involved in terms of any chronic toxicity, biodegradation, distribution inside the body, etc. must be evaluated in-depth to assess the clinical applications.
(5) The animal model studies reported in the literature is mainly focusing on small animals, future work must be based on pigs or primates to advance a step further towards the mainstream application of CNTs.
(6) Macrostructures of CNTs such as aerogel, films, or fibers are one of the best alternatives to overcome the practical problems of utilization of nanomaterials in mainstream applications. Such macrostructures must be characterized in-depth to understand their role in toxicity and biosafety and further can be exploited for real applications.

9 Conclusions

Nanotechnology has come up to become the most trending industry in the current scenario, of which CNTs have been proven to be the most widely applicable in several fields and applications. CNTs are seen to be the most versatile and promising materials in the biomedical field. In this review, we have discussed the methods of synthesis of

CNTs among which chemical vapor deposition (CVD) is widely used. Functionalization of CNTs with biocompatible reagents helps to enhance solubility and suppress toxicity. Functionalization has played a huge role in the advancement of CNTs and their industrial application. CNTs possess great properties such as mechanical, electrical, and optical which help expand their scope for applications. Various applications such as drug delivery, biosensors, bioimaging, tissue engineering, and cancer treatment have aroused in the past few years. In drug delivery, controlled release of Cisplatin gives up to 84.56% anticancer activity at a pH of 6.5. In addition, CNTs functionalized with graphene oxide (GO) act as a great multifunctional material in bone and cartilage tissue engineering which can regulate the cartilaginous and osteogenic abilities of stem cells. In bioimaging, SWCNTs are used which can detect noise equivalent to 7 picograms. Recent studies show that SWCNTs in biosensors can detect SARS-CoV-2. The toxicity of CNTs is an issue that cannot be overlooked and should be taken into consideration while production and its application in the biomedical field. A prolonged accumulation of CNTs in the body can cause various long-term side effects; however, these situations can be administered by the removal of CNTs after the completion of their intended task and also by confining them in non-biodegradable hydrogels to restrict their scattering in the organism.

Apart from these advances, one of the biggest challenges in terms of the economics of CNTs is maintaining the purity and manufacturing it at cheaper rates in huge quantities is required due to its vast applications. To overcome this issue some techniques like CVD have been developed in the recent past which give purer and defect-free CNTs at much cheaper rates. Many researchers are working on developing new processes to increase purity while considering the cost of production and it is expected that better technologies would be developed in a few years which can fulfill our requirements.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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