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Highlights

- CNTs, a one-dimensional carbon allotrope, penetrate particular cellular targets, enhancing drug molecule pharmacological and therapeutic potential.
- The study highlights the importance of carbon nanomaterials, in improving targeted medication delivery systems, overcoming constraints including low bioavailability and unpleasant side effects
- The study explores novel CNT-based anticancer therapeutics, including photothermal therapy, which targets and ablates tumors using near-infrared laser stimulation, resulting in better survival rates in experimental mice
- CNTs can modify genes by introducing DNA molecules into cell nuclei, which is crucial for treating chronic or inherited diseases

Exploring the Potential Application of Single-Walled Carbon Nanotubes in Medical Treatment and Therapy

Sandra Ross Olakkengil Shajan[1], Nandini Markuli Sadashivappa[2], Devaraj Hanumanthappa[2], Shivaraj Kumar Walikar[1], Basavana Gowda Hosur Dinesh[2], Bandral Sunil Kumar[2], Selvaraj Kunjiappan[3], Panneerselvam Theivendren[4], Santhana Krishna Kumar Alagarsamy[5], Kumarappan Chidamabaram[6], Damodar Nayak Ammunje[1*], Parasuraman Pavadai[2*]

[1]Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Banglore-560054, Karnataka, India

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Banglore-560054, Karnataka, India

[3]Department of Biotechnology, Kalasalingam Academy of Research and Education, Krishnankoil - 626126, Tamil Nadu, India

[4]Department of Pharmaceutical Chemistry & Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai, Tamil Nadu 600117, India

[5]Department of Chemistry, National Sun Yat-sen University, No. 70, Lien-hai Road, Gushan District, Kaohsiung city-80424, Taiwan

[6]Department of Pharmacology, College of Pharmacy, King Khalid University, Abha 62529, Saudi Arabia

*Correspondence:

Dr. Parasuraman Pavadai, Email: pvpram@gmail.com

Mr. Damodar Nayak Ammunje, Email: superdamu@gmail.com

ABSTRACT

This comprehensive review highlights the potential of carbon nanotubes (CNTs) as versatile nanomaterials in medicine by exploring their numerous therapeutic applications. The synthesis processes for single-walled and multi-walled carbon nanotubes are explored in detail in this article, which includes flame synthesis, arc discharge method, laser ablation, nebulized spray pyrolysis, and chemical vapor deposition method. The article focuses on the unique physiochemical characteristics of CNTs that make them attractive for a range of biological uses, including genetic engineering, infection therapy, antibiotics, antibacterial treatments, and anticancer therapies. This article also examines the potential use of CNTs in tissue regeneration and artificial implantation, as well as their use as medications and drug delivery vehicles. The importance of functionalized carbon nanotubes in improving biological applications- such as tissue engineering and infection treatment-is emphasized in the study. Furthermore, it also discusses the possible drawbacks and toxicity issues related to the application of CNTs, highlighting the need for more studies to guarantee their safety and efficient application in therapeutic contexts.

Keywords: Carbon nanotubes, nanocarriers, antimicrobial activity, Cancer

1. INTRODUCTION

Targeted drug delivery, a method designed to deliver medication to specific diseases or organs for an extended period, has emerged as a revolutionary approach in medicine. This precision targeting minimizes the impact on nontarget cells, ensuring desired therapeutic effects without unwanted side effects[1]. Nanotechnology plays a pivotal role in enabling targeted drug delivery, offering significant advancements in global healthcare and various fields, including medicine and genomics[2]. Conventional drug delivery systems face limitations such as poor bioavailability, a lack of sustained release, and undesired side effects [3]. Carbon nanomaterials, a key player among nanomaterials, serve as effective carriers facilitating direct penetration of drug moieties into specific targets, and they address these challenges by delivering precise amounts of drugs, penetrating specific cell cytoplasm or nuclei [4]. This capability enhances the pharmacological and therapeutic potential of drug molecules[5]. Carbon nanotubes are unique allotropes of carbon with a 1D structure formed by rolling up carbon nanotube sheets, exhibit Sp2 hybridization in the middle, and feature pentagonal and hexagonal rings at the ends.

Their unique characteristics make them attractive choices for effective medication delivery systems. With a wide surface, they can hold a large number of drug molecules, which is advantageous for longer-acting or higher-dosage drugs [6]. Carbon nanotubes can also be modified or functionalized by adding certain substances, such as peptides or antibodies. By making it possible for medications to be efficiently delivered to certain cells or tissues, increases therapeutic efficacy and reduces adverse impacts on healthy cells [7–12]. Additionally, hydrophobic drugs are frequently poorly soluble-can be encased in nanotubes, greatly increasing the likelihood that they will be administered [13].

2. SINGLE-WALLED CARBON NANOTUBES

One of the allotropic forms of carbon is single-walled carbon nanotubes (SWCNTs), a quasi-1D material. Among one-dimensional nanomaterials, carbon nanotubes are special because they can bind a variety of substances, including DNA, fluorescent compounds, and deadly poisons. The two main types, including single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNTs), have distinct characteristics [14]. Vander Waals interactions hold SWCTs together to create a one-dimensional structure that has a diameter of 1-2 nm and looks like rolled graphene sheets. In contrast, MWCNTs consist of many layers with broader interlayer gaps and have inner and outer diameters of 1-3 nm and 1-50 nm, respectively [15]. Both types have graphene sheet caps at their ends. Graphene is a sheet of carbon atoms that varies from 0.4 to 5nm. It may be conceptualized as neatly rolled hollow cylinders.

The exceptional mechanical, optical, thermal, electrical, and optical properties of these nanostructures have spurred extensive worldwide research. CNTs can have a wide range of qualities, depending on how they are assembled from individual carbon atoms. The most common approach for characterizing them depends on how the expected graphene sheet is folded [16–27].

3. SYNTHESIS OF SWCNT

3.1 ARC DISCHARGE TECHNIQUE

Arc discharge techniques are used to create single-walled CNTs, and graphite rods are necessary for these processes. The device consists of a chamber that houses the cathode and anode, and two vertically orientated graphite rods. Carbon molecules that originate from rods and metal catalysts such as cobalt or nickel evaporate throughout the process. The arching process is then started by applying a direct current to the chamber. After that, the chamber is heated to around 4000K and then pressurized. Around fifty percent of the evaporated carbon solidifies at this phase and forms a deposit on the cathode tip at a rate of 1mm/min. notably, the process involves a progressive consumption of the anode[28]. The arc discharge method may be used to generate SWCNTs in two main ways, each of which uses catalyst precursors differently. While the second method requires no catalyst precursor at all, the first strategy makes use of a variety of catalyst precursors. Several catalyst precursors and a sophisticated anode consisting of metal and graphite are utilized in the discharge expansion method to generate SWCNTs. More specifically, catalyst precursors are usually not required for the synthesis of multi-walled carbon nanotubes. The primary advantage of arc discharge technology is its capacity to produce a large number of nanotubes[29]. The main drawback is the use of high temperatures, which produce SWCNTs with fewer defects, but with less alignment control. Purification is necessary because of the metallic catalyst used in the process [30].

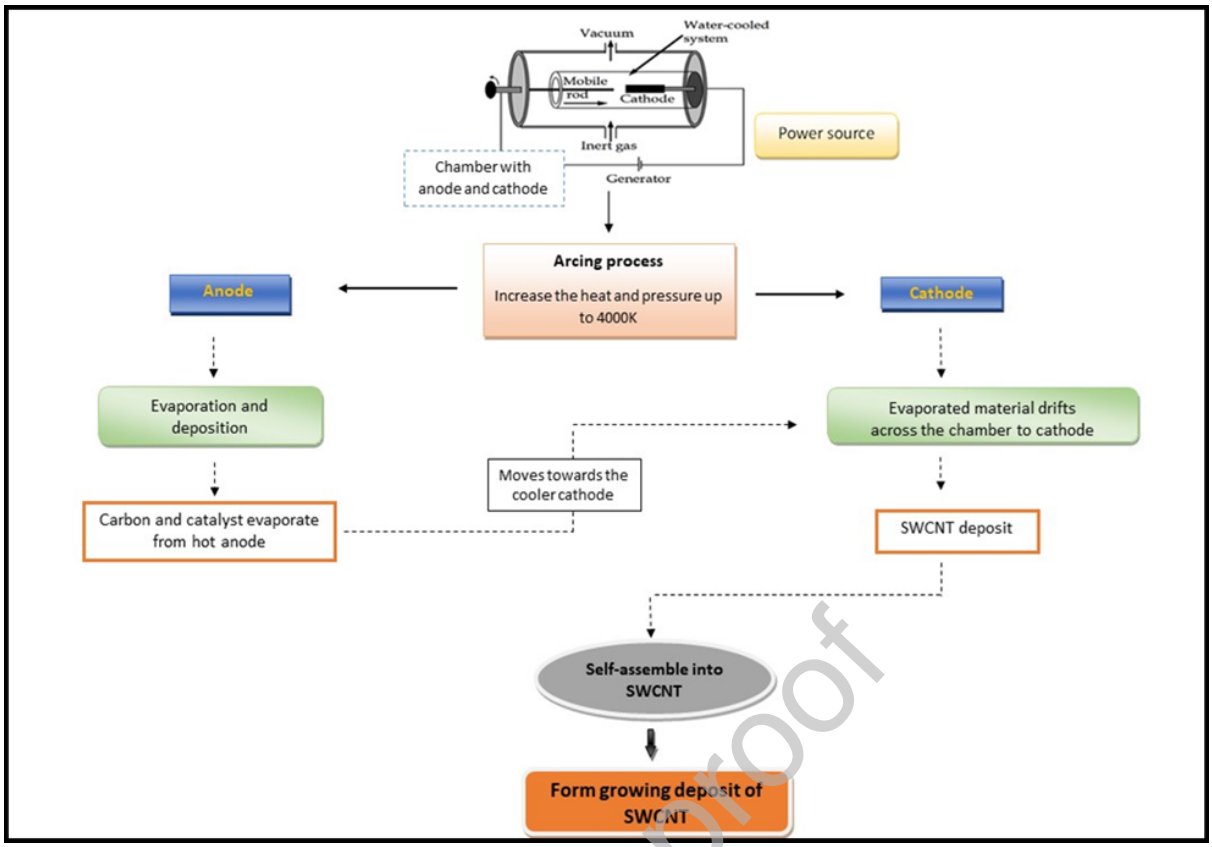

Figure 1: Schematic progress of CNT formation by the arc-discharge method [31,32]

3.2 LASER ABLATION METHOD

Single-walled carbon nanotubes (SWCNTs) can also be formed via laser ablation, which involves evaporating a graphite object in a heated, nonreactive environment[33]. The kind and quantity of products that are generated depend on several factors, including the reaction temperature. Small amounts of metals such as Ni, Co, or Fe are added to the carbon substrate resulting in the formation of SWCNTs[34]. Some benefits of this technique include decent high-yield quality SWCNTs and the flexibility to change both the size and distribution of carbon nanotubes by adjusting different parameters. However, there are disadvantages, such as the possibility of branching and imperfectly straight CNT manufacturing. Even with pure graphite rods and strong lasers, laser ablation may produce fewer CNTs than the arc discharge process. But still large volumes of SWCNTs with good structure can be produced using both the arc-discharge and laser-ablation processes, although they both need a lot of energy and specialized equipment. Given that they require less CNT purification, gas phase methods, such as chemical vapor deposition (CVD), are recommended as more productive options in terms of yield and purity. Although MWCNTs can also be produced under specific reaction circumstances, the laser ablation process promotes the formation of SWCNTs [35–38].

3.3 CHEMICAL VAPOR DEPOSITION TECHNIQUE

Chemical Vapor Deposition (CVD) is a regular method for the large-scale production of carbon nanotubes[39]. CNTs develop on the outer layer of the catalyst particles as a result of the breakdown of the carbon precursor. Thermal CVD and plasma-enhanced CVD constitute two of the primary CVD methods used to produce CNTs [40]. Additional techniques include microwave plasma, hot filament CVS, radio frequency CVD, and water-assisted CVD. We may use this technology to produce the necessary types of CNTs[34]. The production of SWCNTs is primarily determined by the growth temperature, catalyst, hydrocarbon supply, and reactor environment. MWCNT synthesis usually takes place at temperatures between 600 ^{0}C and 900 ^{0}C, whereas SWCNTs evolve at temperatures higher than 700 ^{0}C [41].

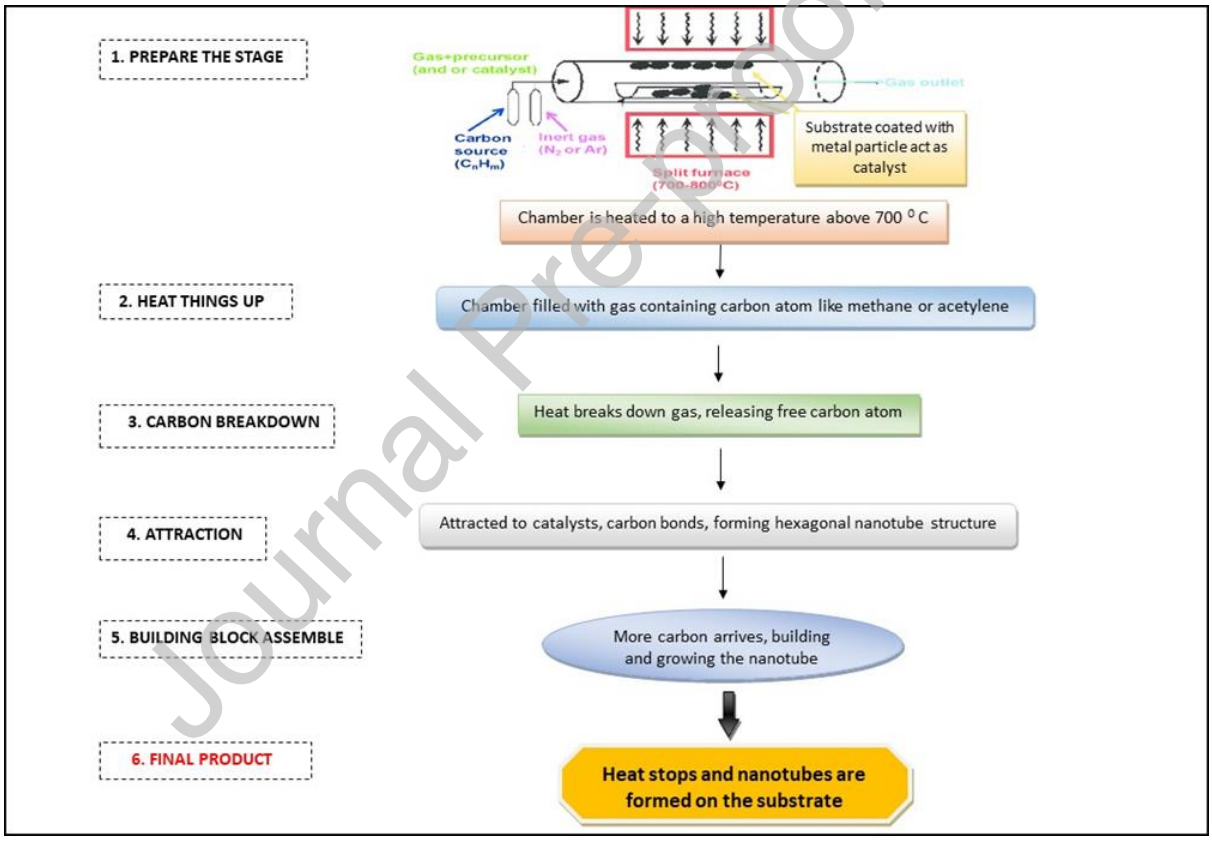

Figure 2: Diagrammatic progression of the Chemical Vapor Deposition technique for CNT production [42]

3.4 FLAME SYNTHESIS METHOD

A heated-up, carbon-rich environment gives rise to a fuel-rich flame. The system may be favorable for the synthesis of nanotubes if transition-metal compounds such as Fe or Ni are added. As a result, flame synthesis is a scalable, continuous-flow process that can create

nanotubes at a much lower price than competing methods[43]. By using flame synthesis, carbon nanotubes are produced with unique characteristics that are not possible with existing synthetic techniques. The flame synthesizing method is particularly remarkable since it yields remarkably quick residence times for both catalytic start and nanotube development [40]. Rich carbon sources, including CO, CH_4, C_2H_4, and C_2H_6, can be found in the post-flame zones. The heat produced by the chemical energy in the flame drives the exothermic reactions that lead to the deposition of carbon, and catalysts [44] are also required for supplying reaction areas for the accumulation of solid black carbon [34].

3.5 NEBULIZED SPRAY PYROLYSIS METHOD

Nebulized spray pyrolysis is a crucial step in this process that involves using a specialized ultrasonic atomizer to create a nebulized spray[34]. This method has been used to develop MWCNTs in aligned bundles with somewhat homogeneous diameters [45,46,47]state that this procedure involves spraying a mixture including the carbon source, solvent, and catalyst into a tube furnace at a constant temperature of 800 ^{0}C while keeping an argon flow rate of1L/min[34,47]. Ethanol is widely used as a solvent and carbon source due to its low cost, ease of handling, and lack of production of toxic byproducts such as carbon monoxide [34]. The advantage of utilizing a nebulized spray in this process is its ease of scaling up to an industrial size, as reactants are continuously delivered into the furnace. With this method, it is possible to produce high growth of MWCNTs on a surface [34,48].

Table 1 presents a comparison between the following methods of carbon nanotube synthesizing: arc discharge, laser ablation, CVD, flame synthesis, and nebulized spray pyrolysis.

FEATURES	ARC DISCHARGE	LASER ABLATION	CVD	FLAME SYNTHESIS	NEBULIZED SPRAY PYROLYSIS
Process type	High-temperature arc between electrodes	Laser evaporation in hot atmosphere	Gas phase growth on the substrate	High-temperature, carbon-rich flame	Atomized spray injection into high-temperature chamber

Scale	Scalable for large-scale production[49]	Small-scale research and development, potentially scalable	Scalable for large-scale production[49]	Scalable and continuous-flow	Potentially scalable for industrial usage
Cost	Moderate initial investment, relatively simple setup	High initial investment for equipment and laser expertise	High initial investment and complex processes	Can be significantly lower than CVD and traditional methods	Relatively low cost and simple setup
Control over SWCNTs	Moderate control over diameter and distribution, primarily SWCNTs with catalyst precursors	High control over size, distribution, and chirality	High control over type, size, and distribution	Less control compared to CVD, primarily MWCNTs	Moderate control, potential for aligned MWCNTs
Typical temperature	Around 4000K	Hot atmosphere (above 1000^0 C)	Above 900^0 C for SWCNTs	High-temperature flame (over $1000\ ^0$C)	$800\ ^0$ C in furnace
Carbon precursor	Graphite rods	Graphite target + metal catalysts	Various hydrocarbons	Fuel-rich flame	Ethanol and ferrocene solution
Catalyst	Required for SWCNTs (Ni, Co, etc.)	Optional for SWCNTs, metal catalysts for control	Crucial for SWCNT growth	Transition metals like Ni, Fe	Ferrocene (catalyst precursor)

Advantages	High yield	High quality SWCNTs, precise control over properties, flexibility	High purity and controlled properties, scalable	Low-cost continuous production, unique CNT properties	Scalable, simple set up, potential for aligned MWCNTs
Disadvantages	High energy consumption, less control over alignment, purification required	Lower yield compared to arc discharge, requires specialized equipment, may produce non- straight CNTs	High initial investment, complex processes, less control over MWCTNs	Less control over SWCNTs, safety concerns with flame	Moderate control, limited SWCNTs types

4. BIOMEDICAL APPLICATIONS OF CNTs

4.1 CARBON NANOTUBES FOR INFECTION THERAPY

CNTs have been tested to address issues caused by infectious pathogen resistance to a variety of antiviral and antibacterial medications, as well as the body's inefficiency with some vaccines[50,51]. It has been shown that functionalized CNTs can serve as carriers for antimicrobial substances such as antifungal amphotericin B [52,51]. Amphotericin B can bind covalently to carbon nanotubes and be transported into mammalian cells. When this conjugation is compared to the free drug, the antifungal toxicity has been lowered by roughly 40%[50]. Research indicates that the effective combination of amino-MWCNT exhibits significant adsorption, and the antibacterial drug pazufloxacin mesylate will be used in experimental testing to treat infections [53]. In addition, functionalized CNTs can be used as a vaccine delivery system[53,54]. When a bacterial or viral antigen is bound to CNTs, the shape of the antigen is preserved, triggering an appropriate and specific antibody response[55]. Functionalized CNTs can be fixed with B and T cell peptide epitopes to create a multivalent system that can mount a powerful immunological response, making it a promising option for vaccine administration [51 ,56,57].

The administration of antisense treatment has been proposed to be a promising approach to the treatment of infectious disorders. The lipophilic characteristics of biological membranes pose a significant obstacle to gene therapy, as they limit the intracellular transport of foreign substances. In fact, SWCNTs can pass through cell membranes. Chemically functionalized SWCNTs with poly (diallyl dimethylammonium) chloride (PDDA) and hexamethylenediamine (HMDA) to produce a composite material to negatively charged siRNA through electrostatic interactions[58]. In earlier experiments, doses of up to 10mg/L of PDDA-HMDA SWCNTs had minimally harmful effects on isolated rat heart cells[59, 60–62]. Extracellular signal-regulated kinase (ERK) siRNA in this drug delivery system, which allowed it to pass through the cell membrane and reduce the expression of target ERK protein in primary cardiomyocytes by around 75% [63].

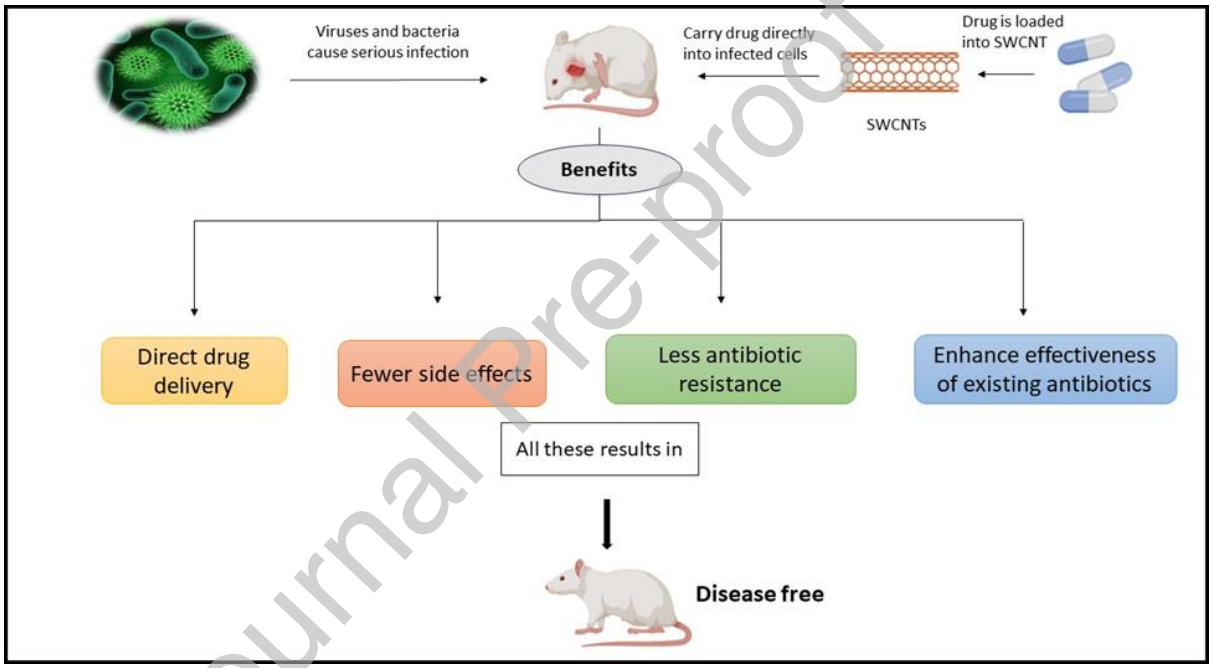

Figure 3 Carbon nanotubes demonstrate promising potential for infection therapy by serving as carriers for vaccine delivery systems, improving therapeutic efficacy, and reducing adverse effects on healthy cells.

4.2 ANTIFUNGAL DELIVERY

Amphotericin B is detrimental to the kidneys and liver and is unaltered and excreted, and several formulations have been created for this drug. CNTs are an excellent choice for the delivery of antifungal medications due to several properties. Amphotericin B retained a very high level of antifungal action when transported by CNTs. Conjugated amphotericin B with CNT has been proven to be more effective against candida than the medication itself. Furthermore, it was demonstrated that there was a dose dependence in the internalization of

amphotericin B associated with the nanotubes. Furthermore, it was demonstrated that there was a dose dependence in the internalization of amphotericin B associated with the nanotubes [64–67]. Functionalized CNTs exhibit the behavior of nanoneedles and may cross the cell membrane barrier without harming cells, as demonstrated by Wu et al. He has proposed that another benefit of CNTs is their ability to avoid the phenomenon of aggregation that amphotericin B generally exhibits in solution, which may otherwise exacerbate the drug's cytotoxic effects on cells. Furthermore, it was shown that conjugated amphotericin B in conjugation with CNT was not toxic at doses as high as 10 10μg/mL. Through an unknown mechanism, functionalized CNTs containing amphotericin B demonstrated efficacy even against strains resistant to the drug [68].

4.3 ANTIMICROBIAL APPLICATION

The microorganism membrane and cell wall have been impacted by CNTs[69]. Moreover, CNTs can expose a cell to oxidative stress, which ends in biological death. Because the material has a higher surface area per unit volume, superior electrical conductivity, high transparency, and structural stability, its antibacterial activity rises as it approaches the nanoscale[70,71]. Physical and chemical factors are combined to create the fundamental mechanisms of SWCNT's bactericidal effect[72–74]. The cell wall and membrane of the microorganism may sustain significant structural damage as a result of CNTs[75]. Furthermore, they possess the ability to physiologically isolate cells from their surroundings, which eventually leads to the formation of hazardous materials like reactive oxygen species and exposes the cell to oxidative stress, ultimately causing its demise[76]. Determining the length of the nanotubes during their contact with the cell membrane is unquestionably crucial[77]. It is established that the shorter tube performs better against bacteria than the longer CNTs[78]. According to another research investigation, CNTs elevate the class II major immunological compatibility complex (MHC) to improve the specificity and sensitivity of the antibody-based response[79,80]. In addition, CNTs have been shown to have a significant impact on antibacterial activity by inducing the glutathione antioxidant to undergo oxidative stress, which in turn kills infectious pathogens by increasing the oxidative stress on bacterial cells[81–84].

4.4 ANTI-BACTERIAL APPLICATION

Antibiotic-resistant bacterial species are becoming a bigger concern despite recent advances in antibacterial treatment. The overuse and abuse of antibiotics, as well as the delay of the pharmaceutical industry in presenting new, potent antibacterial medications, were the root causes of this problem. In this sense, the combination of CNTs with antibiotics may be a useful

way to address these issues and enhance antibacterial treatment[85,86]. To address these issues and improve antibacterial therapy, the use of CNTs in conjugation with antibiotics could serve as a promising option [87,88]. Multi-walled CNTs treated with vancomycin hydrochloride were developed by Lie et al. The intrinsic carboxyl group of multiwalled CNTs along with the vancomycin-containing amide group reacted to carry out the synthesis. The newly developed CNTs show outstanding antibacterial characteristics that may be used to treat wounds[89]. One well-known antibiotic in the fluoroquinolone class is ciprofloxacin. Gram-positive and Gram-negative bacterial infections have long been treated with ciprofloxacin. On the other hand, ciprofloxacin resistance has been spreading quickly globally[90,91]. Assali et al. suggested a unique type of functionalized single-walled CNTs with packed ciprofloxacin as a solution to this challenge[92]. Transmission electron microscopy (TEM), spectroscopy using Raman spectroscopy, thermogravimetric analysis, and microbiological examination have all been used to analyse the recently produced CNTs. The study findings showed that, compared to the ciprofloxacin-free medication, ciprofloxacin-loaded CNTs significantly increased the effectiveness of their antibacterial properties against the three bacterial strains[93].

4.5 ANTICANCER THERAPIES BASED ON CNT

Using near-infrared (NIR) laser stimulation to activate the photothermal characteristics of CNTs has become a sophisticated way to target cancer directly. Burke et al. showed that directly injecting MWCNT suspension into tumours and then briefly stimulating the tumours with a laser caused tumour ablation in mice, improving their survival [94]. On the other hand, Wang et al. reported the use of single-walled carbon nanotubes (SWCNT) conjugated with anti-CTLA-4 in intravenous injection[95]. This combination of injection and photothermal therapy (PTT) not only induced an immune response but also increased cytotoxic activity [96]The combination of these two methods destroyed any residual nodules or metastases [97].

There have been suggestions to combine PTT with imaging techniques to treat the main tumours and identify associated lymph nodes at the same time[98]. According to Zhu et al.,[99] there has been a notable advancement in the photothermal conversion of hybrids, including MWCNT and gold nanostars, which has enabled a decrease in the duration of laser stimulation during therapy. Furthermore, the use of PTT in conjunction with molecule delivery, as reported by Wang et al. and also employed by Wells et al., broadens the scope of application for this cancer therapeutic approach [100,101] . However, the depth to which laser penetration can penetrate tissues limits the efficacy of CNT-assisted PTT, and it still has to show success for thicker samples[102]. The toxicity of carbon nanotubes (CNTs) on cells during their use has been the subject of numerous studies in this section; however, the ultimate fate and possible

decomposition of these objects have not been fully investigated[95]. When nanotubes are not contained within or on the surface of a device, this issue - which is still debatable - could be a major hindrance to the use of CNT in biomedicine[102,103]

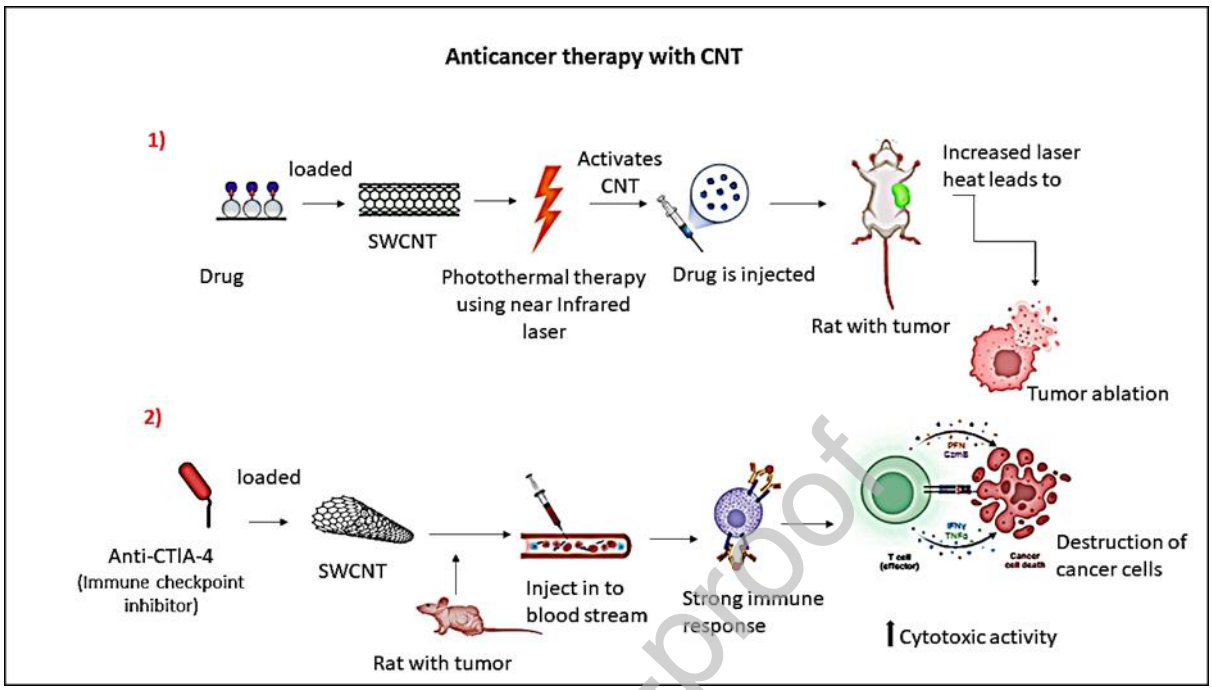

Figure 4 Illustration demonstrates the promising potential for anticancer therapy through the destruction of cancer cells and tumour ablation.

4.6 CNTs for GENETIC ENGINEERING

CNTs are used to modify genes and atoms in the creation of proteomics, tissue engineering, and bioimaging genomes. To replace a damaged gene that contributes to some chronic or inherited diseases, gene therapy involves introducing a DNA molecule into the cell nucleus[34,104] The unravelled DNA coils around the SWCNT and changes its electrostatic property by connecting its specific nucleotides. Single-stranded DNA has been shown to wrap CNTs in a sequence-dependent way, which makes it valuable for DNA analysis. Nanotubes are used as gene carriers to cure genetic diseases such as cancer due to their unique cylindrical shape and properties[105]. Their usefulness as a vector for gene therapy has been proven by their tubular structure. It was shown that DNA complexes with nanotubes released DNA before the defense mechanism of a cell destroyed it, resulting in a significant increase in transfection.

Nanostructures have shown an antiviral effect against the respiratory syncytial virus, which causes asthma and severe bronchitis. Treatment usually consists of a combination of nanoparticles and gene-slicing techniques. RNA snippets wrapped in nanotubes that can inhibit a protein are administered via nasal sprays or drops. There are reports of protein helical crystallization using nanotubes and rat embryonic brain neuron growth[106].A recent study

reported a novel CNT-based technology that supports cell development and enables fast, high-efficiency gene transfection into cells via CNT lumens. Propidium iodide, which has a molecular weight of 0.66 kDa, is the smallest biomolecule of the size that this device can accommodate. Furthermore,[107] reported the presence of tetramethylrhodamine dextran at 3 kDa and 6000 bp of plasmid DNA at 3900 kDa. It was also proposed that the usage of nanocarriers based on MWCNTs and SWCNTs may be used to carry genetic material to callus cells, leaf explants, and mesophyll protoplasts. Consequently, CNTs have been shown to be useful in the agricultural alteration of plant genetics [108].

4.7 USE OF CNT FOR DIAGNOSTIC

Improving detection methods is particularly crucial, as successful treatment depends on an early diagnosis. In vitro biomarker analysis is already possible[109] with good accuracy due to immune complex detection; however, using classic dosage approaches can be time-consuming and require large amounts of biological material. Because of their electrical properties, carbon nanotubes (CNTs) have been the subject of much research, leading to the development of numerous label-free CNT-based biosensors. Furthermore, CNT can be used as a contrast agent in a variety of bioimaging methods[109, 110]. They provide a comparatively high degree of spatial resolution in determining the location and presence of certain cells when functionalized and connected to various biomarkers[95].

4.8 BIOSENSORS BASED ON CNT

Carbon nanotubes (CNTs) have been proposed as a sensing element in the field of biosensors to detect and monitor various diseases, specifically diabetes and bacterial infections[111]. For example, Punbusayakul et al. used electrochemical monitoring of immune complexes to identify salmonella, which reduced detection time and simplified sample preparation compared to earlier methods[109,112]. To immobilize DWCNTs, directed antibodies were grafted onto their surface to create an immunosensor for adiponectin, a biomarker of obesity. During the monitoring of cyclic voltammetry, a second antibody conjugated with horseradish peroxidase (HRP)-streptavidin binds to adiponectin and interacts with the substrate, enabling quick detection and quantification[109,113]. Field-effect transistor (FET)-based sensors have demonstrated excellent sensitivity; in fact, Ramnani et al. have recorded sensitivity as low as attomole on occasion[95]. Resistive sensors, more precisely, differential resistive pulse sensors (RPS) based on MWCNT, have recently achieved the single molecule detection threshold, highlighting the wide range of applications for these sensors [109]. Another recent technique has demonstrated the utility of porosity in immobilizing molecules on biosensor electrodes[95].

Zhang et al. reported on a nonenzymatic glucose detector composed of a porous nickel-based metal oxide framework (Ni-MOF) with carbon nanotubes (CNT) added to improve electrical conductivity. Given the high selectivity of these electrodes, the method is proposed as a feasible replacement for immune complex immobilization detection [109 ,114, 115,116].

4.9 ARTIFICIAL IMPLANTATION AND TISSUE REGENERATION

Because of their exceptional mechanical, electrical, and thermal capabilities, carbon nanotubes (CNTs) are useful for strengthening a variety of materials to improve their overall qualities. The goal of tissue engineering is to replace diseased or damaged tissue with biological substitutes that can return the tissue to its normal state. Tissue regenerative engineering and medicine have shown great promise due to significant advances in this sector[117]. With standard implants, post-administration discomfort and implant rejection are frequent problems. However, the distinct characteristics of nanotubes and nano horns, along with their small size, allow them to blend in with other amino acids with ease. Because of this, they can be implanted into prosthetic joints without causing the host to reject them[118]. Among many other materials, including synthetic and natural polymers, for tissue scaffolds, CNTs may be the best option for tissue engineering because they are biocompatible, resistant to biodegradation, and can be functionalized with biomolecules to improve organ regeneration[51]. CNTs can be incorporated into the host's body as additives to strengthen the mechanical strength and conductivity of the tissue scaffolding.[51,119–122] To be precise, composite nanomaterials utilized as scaffolds in tissue regeneration have been effectively created by MacDonald et al.by combining carboxylated SWCNTs with a polymer or collagen[123]. The latest study additionally glanced at other tissue engineering uses of CNTs for tissue engineering, including cell tracking and labelling, detecting cellular activity, and improving tissue matrices. For example, CNTs have been shown to significantly improve the *in vitro* differentiation of neurogenic cells by embryonic stem cells and the regeneration of bone tissue in mice[42,58,124,125].

4.10 CNT AS CARRIER FOR DRUGS AND GENE DELIVERY

Recently, there has been a lot of interest in using CNTs as nanocarriers because of their remarkable ability to facilitate cell transfection. Researcher Liu et al. proved that noncovalent bonding allows drugs like doxorubicin to be loaded onto polyethylene glycol coupled with SWCNTs[126]. This makes it possible to provide medications to tumour tissues using the enhanced permeability and retention phenomenon. A mesoporous silica coating was employed by Wells et al. to load medicines onto CNTs[101]. The alkaline pH at which doxorubicin was

bound to carbon nanotubes reduced its toxicity in healthy body parts, but in the acidic environment of tumour tissues, it was easily released. Wells et al. claim that PEG branches improved the hydrophilicity of SWCNTs and protected bound doxorubicin, increasing the material's stability in blood collection[127]. Another example is the covalent attachment of the anticancer drug 10-hydroxy camptothecin to MCNTs, which may offer a thermostatic approach and exhibit enhanced efficacy[95,128,129]. Genes, proteins, and drugs can be administered intracellularly through carbon nanotubes due to their unique ability to enter cells regardless of functional groups present on their surface. Research in gene silencing treatment applications has grown significantly, particularly with the delivery of short-interfering RNA (siRNA) [130]. Ladeira et al. effectively delivered siRNA to cells difficult to transfect using carboxy functionalized SECNT, resulting in an amazing 96% silencing efficacy [131]. In a separate study, Sanz et al. released DNA both within the cell using chloroquine and outside the cell using polyethyleneimine to transport DNA plasmids into the cytoplasm and cell nucleus utilizing a dual functionalization technique [132].

5. BIODISTRIBUTION

Compared to multi-walled carbon nanotubes (MWNTs), single-walled carbon nanotubes (SWNTs) have a number of advantages, such as their ability to carry huge loads of medications, extend circulation times, and pass-through cell membranes. In addition, SWNTs have inherent qualities such as Raman characteristics, photothermal capabilities, fluorescence, and photoacoustic impacts. They are better for different applications because of their qualities. Biodistribution tests were performed in BALB / c mice with subcutaneously implanted hepatocellular carcinoma SMMC-7721 cells to demonstrate this benefit[133]. Meng et al. used saline solution as a control and administered sliced SWNTs, chitosan-coated SWNTs (CHI-SWNTs), or folic acid-coated CHI-SWNTs (FA-CHI-SWNTs) at a constant dose (around 4 mg/kg)[134,133]. Thirty minutes after injection, mice's urine contained considerable amounts of SWNTs, as shown by transmission electron microscopy, suggesting quick urine clearance[135]. After two hours, fluorescence scans revealed that with low accumulation in tumour tissue, CHI-SWNTs, and FA-CHI-SWNTs were found largely in the liver, heart, and other tissues with an abundant blood supply. However, the enhanced permeability and retention (EPR) effect was shown to be responsible for the strong fluorescence observed in the tumour area after 20 hours, since FA-CHI-SWNT demonstrated particular interactions with tumour receptors[134,133]. CD44 antibodies were used to functionalize SWNT to evaluate their potential to selectively concentrate in breast tumours. In the first few hours after injection, the study found a significant build-up of SWNTs in the organs of the reticuloendothelial system. However, a notable increase

in tumour uptake for CD44 antibody-conjugated SWNTs was seen after 24 hours[136]. These findings demonstrate conjugated silver nanotubes' promising qualities for a range of biological applications, including drug delivery [135].

6. TOXICITY OF CNT

Despite its attractive characteristics, CNT toxicity is a major concern. Studies conducted in vitro and in vivo have linked the toxicity of CNTs to several variables, including concentration, duration of exposure, exposure mode, and even the surfactant employed to disperse the nanotubes[137]. Most of the toxicity features of CNTs are yet unknown, and these discrepancies appear to be mostly caused by variations in the experimental procedure. When the actions of these CNTs are taken into account, this review seeks to examine the representative data on toxicity. A comprehensive assessment of these investigations provides a new understanding of the toxicity of CNTs, focusing on topics such as the frequencies of toxic events, the mechanism of cell damage, and the biodistribution of CNTs according to the organ. Furthermore, this analysis will inspire further investigation into a wide range of topics related to the toxicity of nanotubes[138]. ROS levels in commercial CNTs were higher, increasing oxidative stress and reducing the potential of the mitochondrial membrane. Furthermore, MWCNTs were found to be hazardous to metal impurities, especially at high concentrations. The biological reactivity and toxicity of CNTs are influenced by several physiochemical factors [139,140], such as the method of processing, length, diameter, surface-to-volume ratio, concentration, dispersibility in solution, aspect ratio, degree of oxidation, structure, presence of a functional group catalyst, applied dose, and chemical functionalization [141,142]. Moreover, the toxicity of CNTs has been linked to the length to which they are exposed and the surface utilized in their dispersion [143,144].

6.1 CYTOTOXIC EFFECTS

When carbon nanotubes get inside cells, they lead to oxidative stress, inflammation, and cytotoxicity. This results in the foreign body reaction (FBR) and the generation of free radicals[145]. Physicochemical properties, surface functionalization, length, type, and metal impurities are some of the factors influencing cytotoxicity[139,146]. Menezes et al. reported that uncontrolled exposure to CNTs can cause cell morphological changes, apoptosis, inflammation, oxidative stress, and the development of granulomas[147]. Studies comparing different carbon allotropes reveal that CNTs are more harmful to cells and can trigger immune-mediated cytotoxicity[138,142].

6.2 PULMONARY TOXICITY

Carbon nanotubes, which are used in many products, can be inhaled during production and cause respiratory problems [141,148]. Concerns regarding chronic inflammation and respiratory problems are brought up by their use in food packaging. Pulmonary toxicity is influenced by physiochemical characteristics[138,149]. Research demonstrates that SWCNTs and MWCNTs can cause granulomas and acute and chronic inflammatory reactions [145]. CNTs have a major effect on bacterial clearance, lung function, and the induction of allergic airway inflammation [150].

6.3 CARDIOVASCULAR EFFECTS

Atherosclerosis, cardiac damage, muscle deterioration, and blood flow obstruction are outcomes of cardiovascular toxicity caused by the interaction of CNT interaction with heart cells [145]. The two main factors that induce cardiovascular disease are inflammation and oxidative stress [141]. Research on animals suggests that CNT toxicity can increase the chance of cardiovascular disease by inducing atherogenesis and blood coagulation. Exposure to CNTs has been associated with increased oxidative stress, inflammation, and blood pressure alterations, all of which suggest toxicity to cardiovascular organs[145,148].

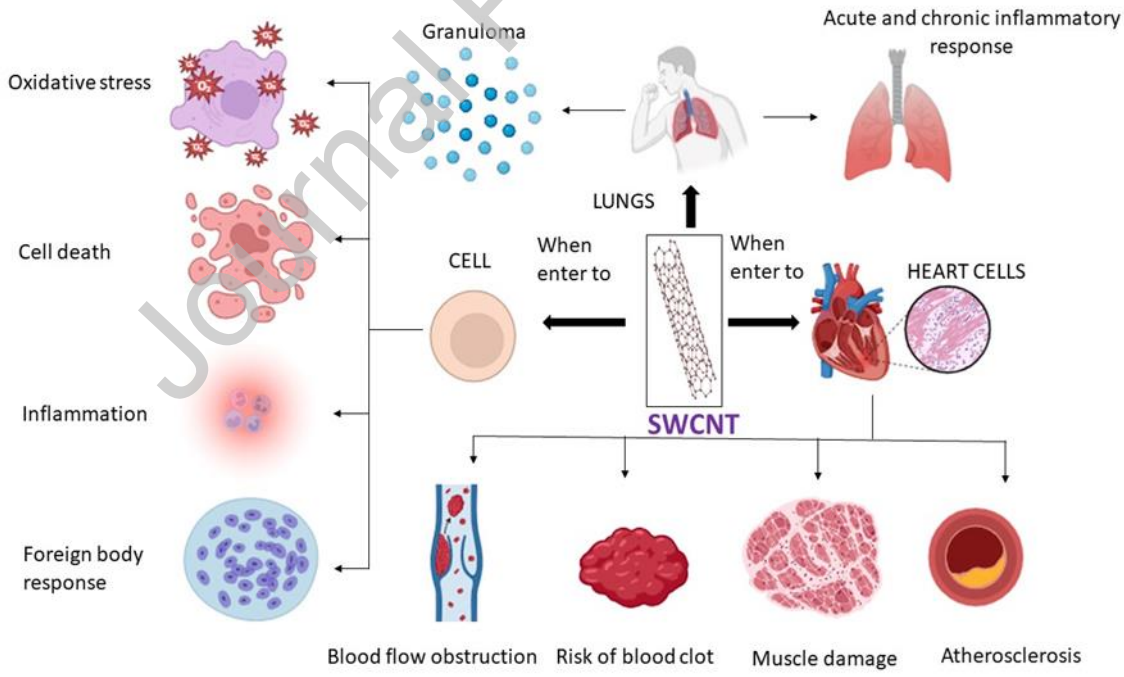

Figure 5 Illustrated the toxicity of carbon nanotubes

7. CONCLUSION

This study provides a comprehensive overview of the wide variety of biomedical uses of carbon nanotubes (CNTs), highlighting the potential and adaptability of these CNTs to enhance multiple aspects of medicine, including cancer treatment, regenerative medicine, and infection therapy. In addition, focusing on the distinctive characteristics of CNTs may be attractive for the advancement of targeted medication delivery, tissue engineering, gene delivery, and antibacterial treatment. This article emphasizes the significant influence of CNTs on these important medical concerns by providing a thorough review of the nanocomposite synthesis techniques and the processes of antibacterial and anticancer therapy. The current study indicates the most effective prevalence of critical applications to determine the safety and performance of CNTs in therapeutic settings.

8. FUTURE DIRECTIONS

Future study avenues to enhance the biomedical uses of carbon nanotubes involve optimizing synthesis techniques to enhance their scalability, economy, and property control. It is imperative to address toxicity and biodistribution in addition to improving targeted drug delivery using innovative functionalization techniques and drug loading mechanisms to guarantee safe clinical use. Important areas of emphasis include infection therapy, tissue engineering, regenerative medicine, combination medicine, and clinical and regulatory translation. Using the special qualities of carbon nanotubes, the biomedical field will be able to create safer, more efficient and more specific treatments, which will eventually lead to better patient outcomes in a variety of medical fields.

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AUTHOR CONTRIBUTIONS

Conceptualization: SR, DNA, PP; literature research: SKW, BG, SKB; writing—original draft preparation: SR, NMS, DH; writing—review and editing: DNA, SK, PT, CK, ASKK; Visualization: PP; project administration: SK, PT, PP. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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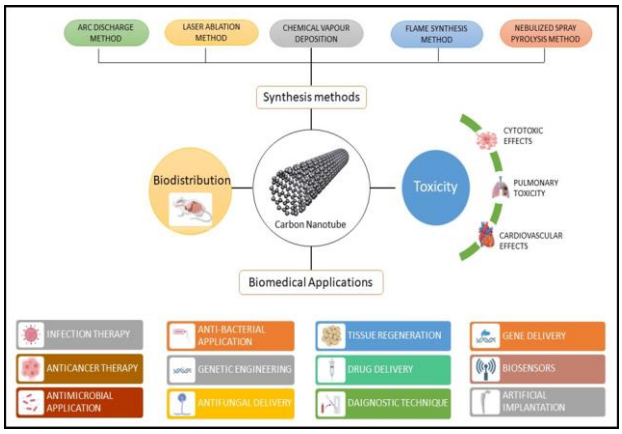
Graphical abstract



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.