Chapter 11
Carbon Nanostructures for Fighting Antimicrobial Resistant Bacteria

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Abstract Various diseases have existed among the humans for a very long time. Humans, since ancient times, have devised different methods/medicines to prevent and cure various ailments from different diseases by bacteria. Nowadays due to the advancement in science and healthcare, various antibiotics have been developed to tackle these diseases and the disease-causing microbes. Various antimicrobials are coming at a rapid pace; they have brought new challenges to the human race. Many bacteria have developed resistance to the antimicrobials which have caused mortality in many individuals and also resulted in serious ailments like *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, etc. These microbes have developed resistance to many medicines by various antimicrobial resistance mechanisms like biofilm formation, modifying the active agent of the medicine, etc. Antimicrobial resistance bacteria are a global concern, and to counter effect this issue, nanotechnology has been given consideration.

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Carbon-based nanostructures have proven to be effective in tackling antimicrobial resistance. Due to their various advantages like small size, modifiable properties by engineering methods, etc., they have been utilized widely as drug delivery vectors, therapeutics, etc. Moreover, the effectivity and cost-effectiveness of in vitro and in vivo studies have been proven. Thus, the introduction of nanotechnology has given a new perspective for tackling antimicrobial resistance.

Keywords Diseases · Healthcare · Nanotechnology · Antimicrobial resistance · Bacteria · Microbes · Carbon nanostructures

11.1 Introduction

Pharmaceutical firms and researchers are looking for novel antimicrobial medicines as a result of the rise of infectious illnesses caused by various pathogenic microorganisms. Humans are highly irritated and poisoned by several antibacterial agents (Varghese et al. 2013). The development of novel antimicrobial agents that are effective, resistant-free, low-cost, and of natural origin is of great importance (Miethke et al. 2021). Antibiotics work by restricting or eliminating microorganisms in a bacteriostatic or bactericidal manner (Kohanski et al. 2010). These medicines work by forming a connection with any important microbial metabolic components and by stopping pathogens from forming functioning biological molecules (Belkaid and Hand 2014). In the current situation, these microorganisms are acquiring resistance to antibiotics, due to which there is a decrease in their efficiency and increased chances of therapeutic failure (Tanwar et al. 2014). Inherent infections connected with MDR bacteria are intimately linked to the worrisome global rises in morbidity and death caused by medication resistance that arises via natural selection (Mocan et al. 2017). Patients are more likely to contract hospital-acquired bacterial infections, which can extend hospital stays and increase mortality rates (Cornejo-Juárez et al. 2015). It was found in the study conducted by Aliberti S. et al. that the patients that were infected by antimicrobial-resistant organisms were found with double hospital stays and an increase in death rates (Aliberti and Kaye 2013). MDR bacteria are a worldwide health concern as they increase the diseased people's morbidity and death rates and affect the clinical outcomes of a wide variety of people in intensive care units, having surgery, transplantation, or cancer therapy (Van Duin and Paterson 2016).

Nanomaterials (NMs) have piqued researchers' interest as a way to overcome the antimicrobial resistance pattern (Munir et al. 2020). These provide an excellent basis for updating the materials' physiochemical characteristics (Fig. 11.1), leading in much more potential antibacterial agents (Hajipour et al. 2012; Verma et al. 2021). Various researchers and scholars are increasingly doing the study on finding the solution for the problem of antimicrobial agents. Some examples of polymeric

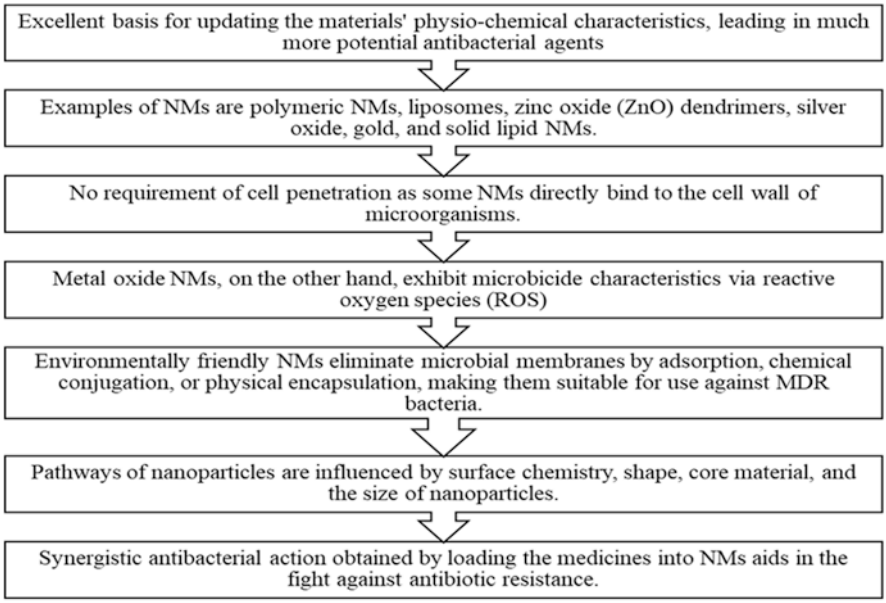

Fig. 11.1 Properties of nanoparticles

NMs are liposomes, zinc oxide (ZnO) dendrimers, silver oxide, gold, and solid lipid NMs (Munir et al. 2020). Some NMs directly bind to the cell wall of microorganisms, thereby eliminating the requirement for cell penetration. Metal oxide NMs, on the other hand, exhibit microbicide characteristics via reactive oxygen species (ROS) (Munir et al. 2020).

NMs have the potential to eliminate the microbial membranes by the process of adsorption, chemical conjugation, or physical encapsulation which makes NMs environmentally friendly for useful against MDR bacteria (Zhang et al. 2010). The pathways of nanoparticles are influenced by their surface chemistry, shape, core material, and size (Gupta et al. 2019; Verma et al. 2018, 2019). Furthermore, the synergistic antibacterial action obtained by loading the medicines into NMs aids in the fight against antibiotic resistance. With these factors, NM-based products play an important role in improving treatment accuracy by interfacing with bacteria‘s cellular system and serving as an antibiotic replacement (Munir et al. 2020). It is a new and promising way to deal with the use NMs in antibacterial treatment to defeat the bacterial obstruction arrangement (Fig. 11.1).

Table 11.1 Highlights the bacterial species causing harm in humans

Species	Damage	References
Salmonella spp., *Campylobacter* spp.	Expanded number of hospitalizations and expanded dreadfulness and mortality	Kaye et al. (2004)
Superbugs having super-resistance gene (NDM-1)	β-Lactam anti-microbials to be enzymatically corrupted render tiny organisms resistant to a wide range of anti-microbials	
MDR *Mycobacterium tuberculosis* (MDR-TB)	Impervious to current antibiotics	

11.2 Antimicrobial Resistant Bacteria: A Global Concern

MDR (Multidrug-resistant) microorganisms are the organisms which are resistant to more than one antibiotic (superbugs). A same microbe can receive varied medication obstruction properties from multiple living forms, leading to the formation of MDR "superbugs." They are posing a worldwide threat and danger to the whole population (Ssekatawa et al. 2020; Makabenta and Nabawy 2021; Munir et al. 2020; Willyard 2017).

Unreasonable utilization of antitoxins has drawn out for cure against MDR microscopic organisms and has been utilized as a prophylactic treatment for different diseases which are the driving reason for opposition (Laxminarayan et al. 2013). These microbes develop resistance to microorganisms by modulating the DNA, RNA and protein combination, biofilm arrangement and restraint of cell divider union to overpower the antimicrobial dangers. Bacteria also possess Mec-A quality that makes the bacteria resistant towards anti-infection agents such as penicillin or penicillin-like anti-microbials and methicillin. There are numerous other ways possessed by the microorganisms that make them impervious to the antimicrobials (Baptista et al. 2018).

For the past 20 years, new kinds of antitoxins are declining at a rapid phase rendering no alternative to treat MDR microorganisms. This has led to crisis circumstances and colossal financial effect. The cases of methicillin-resistant *Staphylococcus aureus* (MRSA) infections have decreased in the United States, Europe, Canada, and South Africa in recent years, whereas MRSA infections have increased in Sub-Saharan Africa, Australia, Latin America (90%), and India (47%) (Chaudhary 2016) (Tables 11.1 and 11.2).

11.3 Antimicrobial Resistance Mechanism

Classification of antimicrobial agents can be done on the basis of antimicrobial activity mechanism. Prominent groups are substance that hinders the synthesis of cell wall, causes depolarization of cell membrane, hinders synthesis of protein, hinders synthesis of genetic material, and hinders pathways adapted by bacteria for

Table 11.2 Indicates the specific bacteria resistant to antimicrobial agents

Infectious agents	Developed antibiotic resistance against	References
Vancomycin-resistant MRSA clinical isolates vanA, vanB, or vanC	Resistant to vancomycin, teicoplanin cross-protection	Begum et al. (2020), Gupta et al. (2019), and Chaudhary (2016)
Staphylococcus aureus strains	Methicillin resistant and resiatant to lactam antibiotics Protection from penicillin	
Enterococcus, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter*	Enhanced antibiotic resistance	
Gram-negative bacteria, Enterobacteriaceae Escherichia coli (CREE. coli)	Carbapenem-resistant bacteria which are capable of restricting antibiotic penetration into the outer membrane Third-generation cephalosporins, ESBLs, and fluoroquinolones	
Gram-positive bacteria, such as *Klebsiella pneumoniae* and *Neisseria gonorrhoeae*	Develop resistance against extended-spectrum beta-lactamases (ESBL) Carbapenems, vancomycin, and third-generation cephalosporins	
Staphylococcus pneumoniae	Penicillin-resistant or non-susceptible (or both)	
Non-typhoidal *salmonella* (NTS) and *Shigella* species	Fluoroquinolone-resistant	
Campylobacter spp.	Quinolones, macrolides, and lincosamides, chloramphenicol, aminoglycosides, tetracycline, ampicillin and other -lactams, cotrimoxazole, and tylosin	
Salmonella	Antibiotic medications, sulfonamides, streptomycin, kanamycin, chloramphenicol, and a portion of the β-lactam anti-microbials (penicillins and cephalosporins)	
Enterococcus faecalis	Penicillin-resistant	

metabolism (Reygaert 2018). Such wide range of mechanisms has given us chance to get better control over the microorganisms, but their improper management has caused resistance issue. Responsible factors are overconsumption of antimicrobial drugs and wrong prescription of antimicrobial therapy (Von Baum and Marre 2005) (Table 11.3).

Categories of resistance mechanism are inactivation or changes in drug, modification of the active site or receptor, alteration in permeability of cell which leads to decrease in drug deposition within cell, and biofilm formation (Santajit and Indrawattana 2016; Reygaert 2018) (Fig. 11.2).

Table 11.3 Mechanisms of antimicrobial class

Mechanism of action	Antimicrobial class
Hinder synthesis of cell wall	β-Lactams Glycopeptides
Depolarization of cell membrane	Lipopeptides
Hinder synthesis of protein	Aminoglycosides, Tetracycline } Binds with 30S ribosomal subunit Chloramphenicol, Lincosamides, Macrolides } Binds with 50S ribosomal subunit
Hinder genetic material synthesis	Quinolones
Hinder Pathways of metabolism	Sulfonamides Trimethoprim

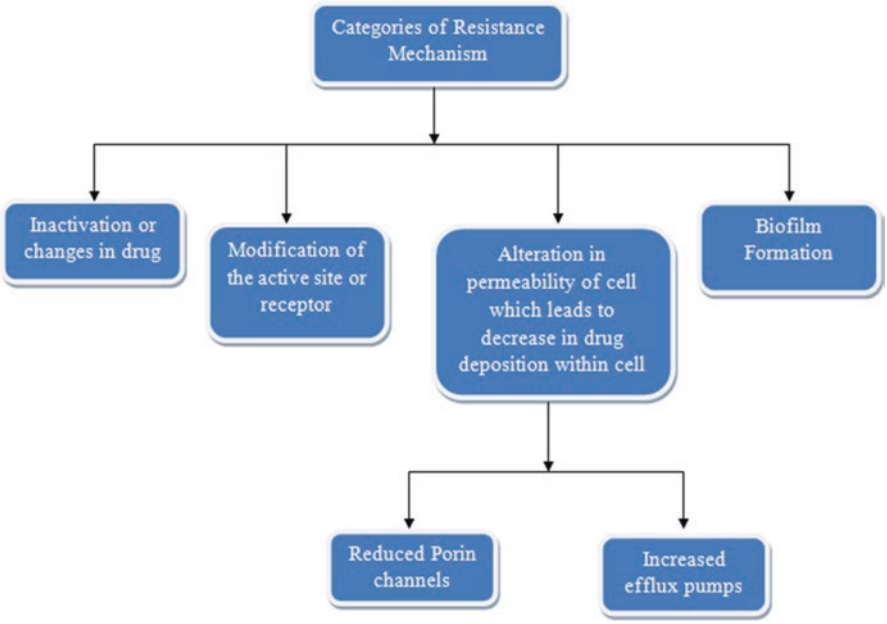

Fig. 11.2 Various categories of resistance mechanism of microbes

11.4 Inactivation or Changes in Drug

Enzymes are produced by bacteria which have the ability to permanently change and deactivate the antibiotics such as β-lactamases, aminoglycoside-modifying enzymes, or chloramphenicol acetyltransferase (Santajit and Indrawattana 2016). Basically there are two pathways for the deactivation of a drug, firstly by the

debasement of the drug and secondly by the shift in the functional group of the drug (Reygaert 2018).

β-lactamases enzymes include penicillinase, cephalosporinase, broad-spectrum β-lactamases, carbapenemases, etc. which hydrolyze the β-lactam ring that is essential for the activity of penicillin, cephalosporin, carbapenems, etc. resulting into their deactivation (Santajit and Indrawattana 2016). Tetracycline is another class of drug which can be deactivated by hydrolyzation.

Most common functional groups that are used for deactivation of drug are acetyl, phosphoryl, and adenyl groups. Most commonly used process is acetylation, i.e., transfer of acetyl group. This is used against aminoglycosides, chloramphenicol, streptogramins, and quinolones. Additionally, phosphorylation and adenylation are also implied against aminoglycoside.

11.5 Modification of the Active Site or the Receptor

There are many target sites in the bacteria where the antimicrobial drug can bind. Similarly, all these sites can be modified to achieve resistance against the drug. This is achieved by gene mutation (Santajit and Indrawattana 2016). For example, β-lactam drugs are mostly used against gram-positive bacteria, and they can achieve resistance by changing the chemical structure of the β-lactam (e.g., PBP2a site in *Staphylococcus aureus* through addition of mecA gene) or by changing the number of PBPs (penicillin-binding proteins). Increase in number of PBPS causes decrement in binding of the drug, whereas decrease in PBPs results in normal drug binding (Reygaert 2018).

11.6 Alteration in Permeability of Cell Which Results in Reduced Deposition of Drug Within Cell

Equilibrium should be maintained between intake and excretion of antibiotic to understand the sensitivity of bacteria to a drug. Decrease in passage of the drug through bacterial cell membrane results in antimicrobial resistance. Mechanisms involved in this are reduced porin channels on the cell membrane or increased efflux pumps (Santajit and Indrawattana 2016).

(i) *Reduced Porin Channels*

Proteins that are present on the cell membrane of the gram-negative bacteria are called porins. These porins serves as channel for the movement of many lipophobic substances such as antimicrobial agents. Decrement in the amount of *P. aeruginosa* porin protein channel OprD leads to reduced entry of drug making bacteria resistance to imipenem drug.

K. pneumonia strains also achieve resistance to β-lactams by loss of porins called OmpK35 and OmpK36 simultaneously along with the generation of certain β-lactamases enzymes.

(ii) *Increased Efflux Pumps*

Bacterial cells have encoded genes for efflux pumps. They are functional either integrally or induced under certain external stimulus. Multidrug efflux pumps exchange high variables of compounds. Efflux pumps have 5 families: ABC family (ATP-binding cascade), MATE family (multidrug and toxic compound extrusion), SMR family (small multidrug resistance), MFS family (major facilitator super family), and RND family (resistance-nodulation-cell division family).

RND works in association with membrane fusion protein and OMP porin to extrude substance throughout the cell membrane. MacB (ABC member) and EmrB (MFS member) act as tripartite pumps and cause efflux of macrolide drugs and nalidixic acid, respectively, resulting into resistance against them in bacteria.

Basically, increased amount of efflux pumps leads to elevated extrusion of the drugs from the cell leading from lesser interaction between drug and receptor causing resistance against antimicrobial agent (Reygaert 2018).

11.7 Biofilm Formation

Biofilms are network-like formation of microbial population as a layer on the extracellular polymeric substances formed by the biofilm on their own. Microbes present in the biofilm can interact with each other as well as with the surrounding. Extracellular matrix consists of polysaccharides, proteins, lipids, and extracellular microbial DNA. Three steps for biofilm generation are adhesion, growth and maturation, and detachment, which can be active or passive.

Biofilm serves as a mechanical and biochemical protection layer which gives a condition required for the activity of a drug. Hence, when the required condition is not achieved, antibiotic cannot enter the bacteria resulting into resistance (Santajit and Indrawattana 2016) (Table 11.4).

11.8 Carbon Nanotubes and Its Antimicrobial Properties

A hollow tube-like structure, having carbon as a structural unit and a diameter less than 1 nm to 50 nm, is known as carbon nanotube. It has a peculiar mixture of rigidity, toughness, and persistence (Mohapatra 1959; Dizaj et al. 2015). CNTs are cheaper and are more potent than the conventional medicine system. For example, transport of amphotericin B to the target site using covalently bonded CNT is inexpensive than the utilization of traditional liposomal amphotericin B (Mocan et al.

Table 11.4 Indicating the various mechanisms of antimicrobial resistance in microbes

Microbe/bacteria	Resistance mechanism	Antimicrobial agent	Reference
Gram-positive bacteria	Enzyme hydrolyzation of β-lactam ring	β-lactam	Reygaert (2018)
Staphylococcus aureus	Enzyme hydrolyzation of β-lactam nucleus	β-lactam	Lowy and Lowy (2003)
	Reduced affinity for PBP	Vancomycin (glycopeptide)	
	Affinity of enzymeDNA complex is reduced by causing mutations in QRDR region	Fluoroquinolone (quinolones)	
	Acetylation or phosphorylation of the drug	TMP-SMZ	
Campylobacter	C257T alteration in the gyrA gene resulting into Thr86Ile substitution in gyrase enzyme	Quinolones	Wieczorek and Osek (2013)
	Alteration in tet(O) gene which is responsible for the formation of ribosomal protection protein	Tetracyclines	
	Changes in 23S rRNA causes mutation in ribosomal target binding site or efflux pump (ABC family)	Azithromycin (macrolide)	
P. aeruginosa, *A. baumannii*, and *K. pneumonia*	Biofilm formation or gene mutation	Penicillin, cephalosporins (β-lactam)	Santajit and Indrawattana (2016)
Mycobacterium tuberculosis	Mutation in rpoB and gyrA genes	Rifampin	Gillespie (2002)
	Mutation in katG, inhA gene	Isoniazid	Dookie et al. (2018)
E. coli	Multidrug efflux systems (RND family) and change in AcrAB-tolC and NorM encoding for porins	Fluoroquinolone	Poole and Poole (2009) and Poirel et al. (2018)
	Alteration in Mef (MF family) or Msr (A) (ABC family)	Macrolides	
	Mutation in Tet gene	Tetracycline	

2017). They have drug transporting property in an effective manner (Azizi-lalabadi et al. 2020).

On the basis of structural layer of nanotubes, they are classified into three forms:

1. SWCNTs – Single-walled carbon nanotubes
2. DWCNTs – Double-walled carbon nanotubes

3. MWCNTs – Multi-walled carbon nanotubes (Azizi-lalabadi et al. 2020; Mohapatra 1959)

These nanotubes have one, two, or multi-layers of carbon cylinders, respectively. The antimicrobial activity of each form varies depending on their shape and surface area. SWNTs can be chair-like, snaky, and chiral dependent. MWNTs are constructed by combining some SWNTs of varying diameter (Mohapatra 1959).

11.9 Synthesis of CNTs

There are three techniques used for the production of carbon nanotubes: arc discharge, laser ablation, and chemical vapor deposition (CVP). In CVP, gases having carbon as composition are decomposed on the catalyst at the temperature less than 1000 °C, whereas arc discharge and laser ablation techniques are dependent condensation process. Solid carbon materials are heated (3000–4000 °C) to vaporize which generates carbon atoms which later gets condensed to form CNTs. Arc discharge technique is utilized for the formation of high-quality MWNTs and SWNTs (Taylor and Shenderova 2012). In this process, CNTs are entrapped along with helium gas in the middle of cathode and anode placed very close to each other. Then DC current is allowed to pass resulting in generation of heat that vaporizes the area of tube and generates small tubes (Azizi-lalabadi et al. 2020) (Table 11.5).

SWCNTs and MWCNTs have effective antagonistic effects for microorganisms irrespective of acute exposure. This explains that CNTs have therapeutic effect. As a toxicity parameter, SWNTs have more toxic effect than MWCNTs towards bacteria.

CNT toxicity level depends on its breadth, area, configuration, surface chemical group, number of coating, etc. The shorter the length of the tube, the higher antibacterial effect it will have as it interacts with microorganism by their open ends leading to additional plasma membrane injury. At solid surface, longer CNTs have less effect than the shorter CNTs. According to research, when MWCNTs extend up to 50 micrometer, the CNT wraps itself across the microorganism and causes osmotic breakdown of it (Al-jumaili et al. 2017).

Table 11.5 Discusses the types of carbon nanotubes and their effects on the various species

Carbon nanotubes	Target organism	Mechanistic action	References
SWCNT	*E.coli*, *S. aureus*	Adhere to bacterial cell wall, cause osmolytic stress on it, efflux of material of cytoplasm	Azizi-lalabadi et al. (2020) and Al-jumaili et al. (2017)
	B. subtilis	Damage to membrane, escape of cellular material, reduced volume of cell, elevated roughness of bacterial surface	
	S. epidermis	Loss of viability of cell causing its deactivation	Al-jumaili et al. (2017)
	S. typhimurium	Aggregation of cells in the form of needles	
	Gram-positive and gram-negative bacteria	Generation of reactive oxygen species	Mocan et al. (2017)
SWCNT-Ag	*E.coli*, *S. aureus*	Interactivity of SWCNTs-Ag with cells, alteration in structure of cell	Azizi-lalabadi et al. (2020) and Al-jumaili et al. (2017)
	Salmonella typhimurium	Mutation of genes responsible for metabolism and integrity of cell membrane	
MWCNT	*E.coli*, *S. aureus*	Adhere to bacterial cell, biofilm	Azizi-lalabadi et al. (2020) and Al-jumaili et al. (2017)
SWCNT and MWCNT	*Lactobacillus acidophilus*, *Bifido7bacterium adolescentis*	Diameter-dependent piercing, length-dependent wrapping	Mocan et al. (2017)
MWCNT-Ag	*E.coli*, *S. aureus*	Adsorption on the bacterial cell wall by producing electrical charges leading to loss of integrity of cell	Azizi-lalabadi et al. (2020) and Al-jumaili et al. (2017)
MWCNT-lysine	Gram-positive and gram-negative bacteria	Positive charge appears on cell membrane because of lysine causing adsorption	Mocan et al. (2017)

11.10 Antimicrobial Properties of CNT and CNT Composites

Antimicrobial property of CNT is because of damage caused to the bacterial membrane when CNT comes in direct contact to it. SWCNTS have powerful antimicrobial mechanism towards *Escherichia coli* as it causes intense membrane damage to bacteria and causes cell death. Decrease in CNT size increases surface to volume

ratio, leading to tight bonding between cell membrane of the bacteria (Azizi-lalabadi et al. 2020). Direct attachment of CNT with the plasma membrane influences its cohesion, breakdown process, and structure of *E. coli*. SWCNTs could penetrate the cell wall at greater degree compared to MWCNTs (Dizaj et al. 2015).

SWCNTs having functional groups –OH and –COOH show better antimicrobial activity towards Gram +ve and Gram –ve bacteria, whereas MWCNTs with –OH and –COOH show negligible antimicrobial activity. Longer SWCNTs cause bacterial cells to aggregate and cause stress on cell wall and also inhibit DNA reproduction (Azizi-lalabadi et al. 2020; Dizaj et al. 2015).

The charges present at the surface of the CNTs are also responsible for the bactericidal effect because it causes oxidative stress in microorganisms leading to interruption in its growth. Diameter is another factor which counts for the antimicrobial activity. CNT with small diameter is more effective as it acts as needle which sticks its one point to the microorganism and coming out to the other end. With larger diameters, CNTs connect to bacteria through side walls. This factor also causes disruption of cell wall as well as DNA and RNA production (Azizi-lalabadi et al. 2020).

CNT composites are formed by the combination of carbon nanomaterial along with biological polymers and nanoparticles like oxides of copper, zinc, titanium, elemental silver, etc. CNM has synergetic behavior with NP like carbon nanotubes-chitosan, carbon nanotubes-Ag, etc. (Table 11.6).

11.11 Conclusions and Future Aspects

Microbes have always been around us; they perform variety of activities and one of them antimicrobial resistance, that is, a global concern. This property has caused many treatments to go ineffective, thus contributing to increases in mortality rates of patients. Carbon nanotubes have revolutionized the scenario of antimicrobial resistance and are giving a new hope to prevent disease and deaths of humans due to this area of concern. The carbon nanotubes have reshaped the antimicrobial issues and have inhibited the growth of various microbes due to their various qualities by formation of ROS, chemical conjugation, high absorption rate, and retarding the respiration functions of microbes, in turn destroying them.

Table 11.6 Briefs about the two main types of carbon nanotubes with their properties and antimicrobial activities

Type of carbon nanotube	Properties	Derivatives	Method of synthesis	Uses	Target species	Antimicrobial effect and mechanism of action	Reference
Fullerene	C60 structure with 20 hexagonal and 12 pentagons with carbon atoms having one π & two σ bonds. Other features include low solubility	Organophosphorus compounds, diphosphates, and phosphonates	Arc discharge method, laser ablation, polyaromatic hydrocarbons irradiated with lasers, carbon laser vaporization	As photovoltaics, antioxidants, biopharmaceuticals, gas storage, for water purification and as catalysts	*E. coli*, *Salmonella* species, *Streptococcus* species, *Pseudomonas putida*, *S. aureus*	Inhibits bacterial growth and metabolism by impairing oxygen uptake by increasing the cyclopropane fatty acids in bacterial cell walls or by reducing the fatty acids in bacterial cell walls causing its destruction	Azizi-lalabadi et al. (2020) and Dizaj et al. (2015)
Graphene	Occurs naturally, 2D structure, crystalline material, that has a high surface to volume ratio with low specific gravity	Expandable graphite (EPG), exfoliated graphite (EFG)	Thermal baking, photoreduction, microwave-assisted reduction and CVD (chemical vapor deposition method)	Drug and gene delivery, cancer remedy, bio-imaging, tissue cell culture procedures	*E. coli*, *Salmonella typhimurium*, *B. subtilis*, *Enterococcus faecalis*	Cause destruction of cell wall and cell membrane by producing ROS by physical destruction and chemical oxidation	Dizaj et al. (2015)

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