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A Perspective on Nanomaterials-Based Therapeutics in Fighting Against Multidrug Resistance (MDR) Bacteria

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Abstract

Nowadays, the antibiotic resistance crisis has become one of the major threats to public health, as it poses a serious medical concern that can lead to millions of fatalities, primarily due to the widespread transmission of resistance by bacterial species resulting in the development of multidrug-resistant (MDR) bacteria. In addition, the increase in MDR infections is also associated with the lack of new and effective antibacterial agents and this has prompted global initiatives to develop more effective antibacterial agents to address the issue. In the past few years, the application of nanomaterials to address this issue has attracted global attention and the development of nanomaterial-based therapeutics has been considered as an innovative strategy to treat MDR infection. For example, their unique and excellent physiochemical properties could enable them to penetrate and disrupt the bacterial cell membrane, resulting in the formation of reactive oxygen species (ROS) that eventually destroy the microbes. In this review, the applications of various types of nanomaterials, such as organic-based nanomaterials, hybrid-based nanomaterials, and inorganic-based nanomaterials, particularly in treating MDR bacteria, are summarized and discussed. Furthermore, the challenges and prospects in the development of these types of nanomaterials for their application as antibacterial agents in the treatment of MDR infections are also discussed.

Keywords Multidrug resistance, nanomaterials, antibacterial

1.0 INTRODUCTION

The emergence of bacterial resistance to antibiotics (Multidrug-resistant bacteria or MDR) has resulted in significant health challenges when it comes to effectively treating stubborn infections (Chinemerem-Nwobodo *et al.,* 2023). The health authorities now classify multidrug-resistant bacteria as an emerging global health crisis, given that the morbidity and mortality of infected patients have significantly impacted individuals in various groups such as intensive care units, those having surgery, organ transplants, or chemotherapy treatment (Exner *et al.,* 2017). It has been reported that the estimated cost for treating patients diagnosed with antibiotic-resistant infections may amount to $50,000, and US $20 billion societal costs annually (Uskoković *et al.,* 2021). Furthermore, the abusive use of antibiotics and the lack of new therapeutics in clinical practice have further worsened this public threat (Uskoković *et al.,* 2021).

Generally, antibiotics such as doxycycline, cephalexin, and metronidazole are examples of common antibiotics used to treat bacterial infections. There are various types of antibiotics, each with different modes of action, and the choice will depend

on the type of infection (Etebu and Arikekpar, 2016). The antibacterial resistance happens when microbes such as bacteria, fungi, and viruses evolve and do not respond to any antibiotics designed to kill them. This has made the infections difficult to treat, thus increasing the risk of severe illness and death (Gautam, 2022). The mechanism of intrinsic resistance may limit drug uptake, inactivate the particular drug, and involve drug efflux, while acquired resistance may modify the drug target, inactivate the drug, and also involve drug efflux (Figure 1). Due to structural differences, both gram-positive and gram-negative bacteria can employ different types of mechanisms. For example, Gram-negative bacteria employ all four main mechanisms, whereas Gram-positive bacteria less commonly limit drug uptake due to the absence of a lipopolysaccharide (LPS) outer membrane and their incapability to use drug efflux mechanisms (Reygaert, 2018).

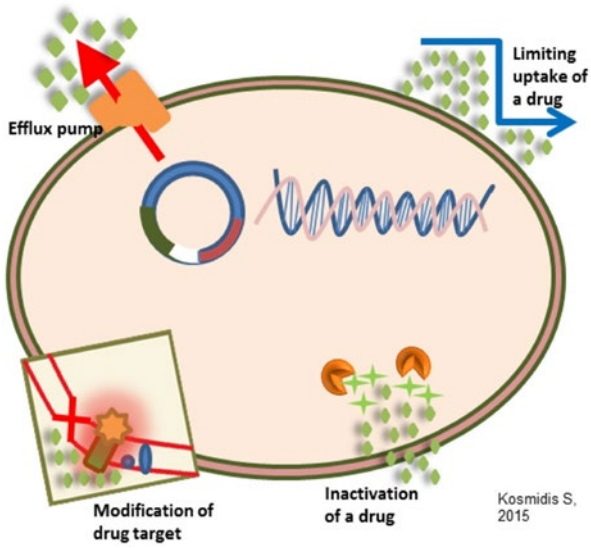


Figure 1 Illustration of the main four types of antimicrobial resistance mechanisms (Reygaert, 2018). This figure was reproduced from an open-access article published by AIMS Press under a Creative Common Attribution license (CC BY).

It is widely accepted that the use of antimicrobials, even when it is necessary and justified, leads to the development of resistance. However, this situation is exacerbated by the widespread unnecessary and excessive use (Ayukekbong *et al.,* 2017). For example, the use of antibiotics without a prescription and availability via unregulated supply chains contributes to this issue (Okeke *et al.,* 2005). In other circumstances, such as when patients experience acute side effects, they tend to abandon the treatment, only returning to the hospital when the infection has worsened. These actions lead to the surviving pathogens being exposed to sub-therapeutic concentrations of antimicrobials thus, increasing the possibilities of developing resistance (Hart and Kariuki, 1998). To make the situation even worse, some patients turn to traditional healers as their treatment option, using herb-drug combinations to cure infections. The main concern is that the unknown substances in the herb-drug combinations may enhance pathogen fitness and contribute significantly to MDR (Ayukekbong *et al.,* 2017).

The most common examples of MDR bacteria are *Neisseria gonorrhoeae* and *Staphylococcus aureus*, both of which are nearly resistant to many antibiotics, including benzylpenicillin. Penicillin was previously applied to cure infections caused by these bacteria (Foster, 2017). Other examples of MDR bacteria are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB), and carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria (Bharadwaj *et al.,* 2022). In addition to these MDR bacteria, the World Health Organization (WHO) has identified 12 families of pathogenic bacteria that could present a significant risk to human health (Mancuso *et al.,* 2021). The WHO has also divided the list into three groups, namely critical, high, and medium, based on the urgency of requiring new antibiotics (Table 1). Unfortunately, the rate of resistance growth in microbes is way more advanced than the development of new antibiotics (Li and Webster, 2018). Hence, designing a new antibacterial material as an alternative to conventional antibiotics is highly recommended.

Table 1 Examples of MDR bacteria listed by WHO are classified into critical, high, and medium categories.

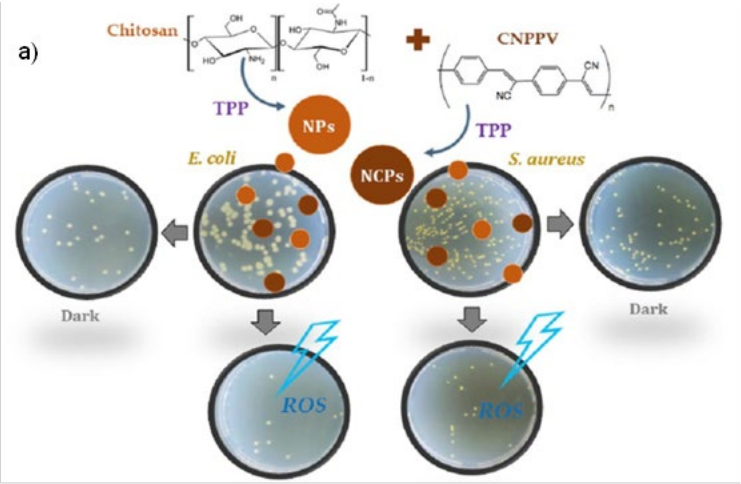
WHO Classification Priority	Bacteria
Critical	*Acinetobacter*, various *Enterobacteriaceae* and *Pseudomonas aeruginosa*.
High	*Campylobacter jejuni, Enterococcus faecium*, *Helicobacter pylori, Staphylococcus aureus*, *Salmonellae*, and *Neisseria gonorrhoeae*.
Medium	*Haemophilus influenzae, Shigella dysenteriae* and *Streptococcus pneumoniae*.

In an effort to fight against MDR bacteria, various new strategies and alternative methods to combat the aforementioned MDR bacteria have been proposed. Such strategies and methods include the development of antibacterial antibodies, bacteriophages, combination antibiotic therapy, and nanomaterials (Naskar and Kim, 2019). Among these strategies,

nanomaterials have gained preference due to their potential to be modified as antibacterial agents without inducing any toxic side effects (Zhang *et al.,* 2010). Recent progress in the application of nanomaterials for combating MDR issues has provided new possibilities in the healthcare system (Makabenta *et al.,* 2021). For example, nanoparticles (primarily in a powdery form which constitute nanomaterials) provide antibacterial mechanisms that are novel to bacteria and therefore, not present in their natural defence mechanisms (Chakraborty *et al.,* 2022). The distinctive physicochemical characteristics of nanomaterials, including dimensions, morphology, and surface chemistry, significantly contribute to their therapeutic efficacy (Zhang *et al.,* 2010). The variation (sizes and shapes) of various nanomaterials resembles bacterial biomolecular components, thus, offering a range of interactions that can be controlled through surface modification. Furthermore, the variation of sizes and shapes of nanomaterials could provide distinctive abilities in targeting the microbes. In addition to size, high surface-to-volume ratios and multivalent interactions are also important factors to consider when preparing antibacterial materials (Gupta *et al.,* 2016). Hence, nanomaterials present a novel alternative approach to providing effective treatment strategies against infections caused by MDR (Makabenta *et al.,* 2021). Generally, the nanomaterials used in biomedical applications can be either organic or inorganic-based materials, and hybrid nanomaterials (D'Lima *et al.,* 2020; Rocha *et al.,* 2022) (Table 2). Figure 2 illustrates examples of various nanomaterial applications in the antibacterial field. In this perspective, how the nanomaterials could be employed to fight against MDR bacterial infections is discussed and summarized. Moreover, the challenges and prospects of utilizing nanomaterials against MDR bacteria are also emphasized.

Table 2 Different types of nanomaterials and their example applications in the treatment of MDR bacteria.

Type of Nanomaterials	Nanomaterials	Bacteria	References
Organic	Chitosan Nanoparticles (Figure 2a)	*Escherichia coli* and *Staphylococcus aureus* bacteria	Facchinatto *et al.* (2022)
	Organic nanoparticles based on a polymer (PDCP-NPs) (Figure 3)	*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* bacteria.	Guo *et al.* (2020)
	Self-assembled fluorescent organic NPs	*Staphylococcus aureus* bacteria	Gao *et al.* (2018)
Hybrid	CoNPs Hybrid and Cu NPs (Figure 2b)	*Enterococcus sp.*	Rodríguez-Otero *et al.* (2023)
	Ag/Ag_2O hybrid nanoparticles	*Pseudomonas aeruginosa* bacteria	D'Lima *et al.* (2020)
	Hybrid tetraamino fullerene with benzothiadiazole fluorophore NPs	*Methicillin-resistant Staphylococcus aureus*	Tan *et al.* (2023)
Inorganic	Carbon nanotubes (CNTs)	*Escherichia coli*	Mohammed *et al.* (2020)
	Graphene-based materials	*Staphylococcus aureus and Pseudomonas aeruginosa.*	Pham *et al.* (2015)
	Carbon quantum dots (CQDs)	*Staphylococcus aureus*	Chai *et al.* (2022)



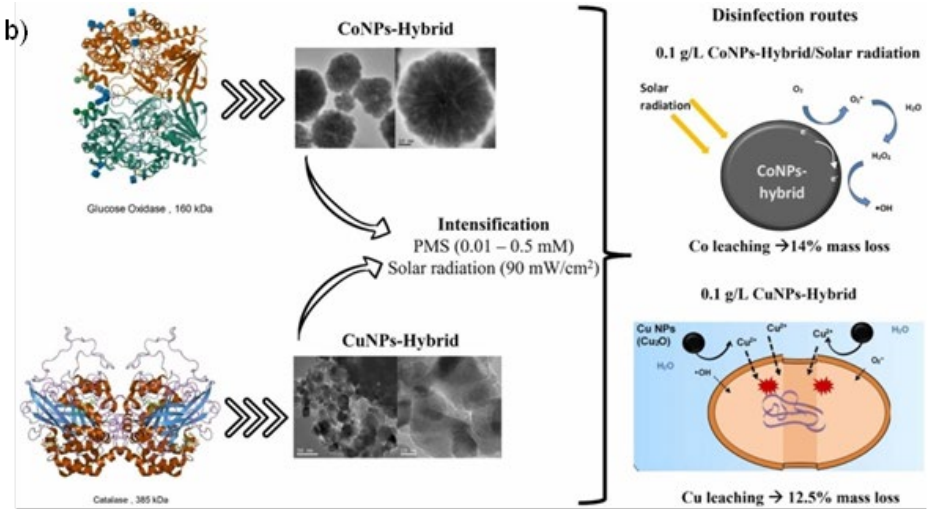


Figure 2 a) Antimicrobial and photoantimicrobial enhancement with CNPPV (Organic-based NPs) addition (Facchinatto *et al.,* 2022) and b) Two nanohybrids of Co and Cu NPs in fighting against *Enterococcus sp.* commonly found in wastewater (Rodríguez-Otero *et al.,* 2023). Figure 2a was reproduced from an open-access article published by MDPI (Basel, Switzerland) under a Creative Commons Attribution Licence 4.0 (CC BY 4.0) while Figure 2b was reproduced from an open-access article published by Elsevier B.V under Creative Commons Attribution Licence (CC BY 4.0).

2.0 ORGANIC-BASED NANOMATERIALS

Nanomaterials derived from organic sources have achieved remarkable advancements in antibacterial treatments due to their enhanced biosafety and the ease of modification through intricate molecular design (Ding *et al.,* 2019). Various functional groups, including but not limited to the amine group, guanidine group, imidazolyl group, 1,2,3-triazole group, and others, have been identified to possess antibacterial activity (Gill *et al.,* 2015). Modifications can be made to these groups to create potent antibacterial substances. Furthermore, the incorporation of nanoparticles into the compounds can greatly enhance the functionality of these groups, particularly in terms of membrane-disrupting actions. Consequently, nanomaterials based on organics have great potential to make a major contribution to combating multidrug-resistant bacteria (Wang *et al.,* 2017).

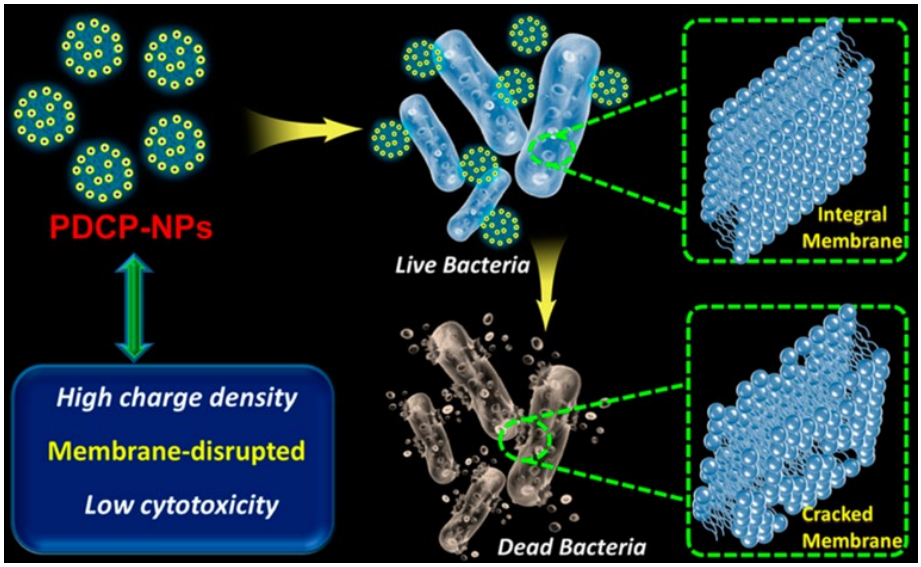


Figure 3 Membrane disruption by organic-based nanomaterial polymer nanoparticles (PDCP-NPs) in antibacterial applications. This figure was reprinted (adapted) with permission from the American Chemical Society, 2020.

The advantage of organic nanoparticles with a high surface area to volume ratio, the organic-based nanomaterials could enrich multiple membrane-binding sites. Furthermore, strategies that involve membrane disruption can be considered an efficient mechanism for destroying bacteria with a lower chance of inducing drug resistance. For example, Guo *et al.* (2020) designed an organic nanoparticle using a polymer composed of a hydrophilic side chain and a hydrophobic skeleton, which was modified with amines to create PDCP-NPs (Figure 3). These components subsequently underwent self-assembly to form

organic nanoparticles. The antibacterial activity demonstrated significant efficacy in both in vitro and in vivo, particularly against gram-negative bacteria such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and ampicillin-resistant *Escherichia coli*. Additionally, the synthesized organic nanomaterials demonstrated low toxicity when exposed to mammalian cells. This finding could serve as inspiration for researchers working in the field of organic-based materials for antibacterial applications, particularly in the development of enhanced membrane-disrupting bactericides (Guo *et al.,* 2020).

However, additional research and development into the modification of organic-based materials are highly necessary to optimize their effectiveness against gram-positive bacteria, considering that the antibacterial activities exhibited slightly lower results compared to gram-negative bacteria. Given that gram-negative bacteria are more challenging to eliminate due to the structural differences in their cell walls, researchers are concentrating on developing antibacterial agents that effectively target gram-negative bacteria without inducing drug resistance (Karahan *et al.,* 2018). However, gram-positive bacteria can still pose significant health concerns, as numerous species are responsible for diseases that necessitate treatment with specific antibiotics (Terreni *et al.,* 2021).

Recently, there has been a notable focus on small molecule self-assembled nanomaterials due to their biocompatibility and versatility in molecular design. In a study by Gao *et al.* (2018), innovative self-assembled fluorescent organic nanoparticles were developed for molecular imaging and the treatment of infections caused by gram-positive bacteria. The self-assembly approach offers a distinct advantage in the creation of organic nanomaterials due to the precision and control it provides. Through careful design of interactions between components, it becomes possible to achieve highly organized and uniformly structured nanomaterials (Wang *et al.,* 2014). Ensuring uniform nanosized particle preparation is crucial, as it reduces the possibility of inducing resistance in cases of drug-resistant pathogens (Xie *et al.,* 2017). The self-assembled fluorescent organic NPs prepared by Gao *et al.* (2018) exhibited remarkable antibacterial activity against *Staphylococcus aureus*, with a minimum inhibition concentration (MIC) of 2.0 mg mL^{-1}. The nanomaterial was prepared by the combination of tetraphenyl imidazole core and quaternary ammonium group (TPIP) to prepare a cationic bola-type small molecule (TPIP-FONs). Interestingly, the respective prepared organic-based nanomaterial demonstrated favourable biocompatibility with mammalian red blood cells (RBCs). Thanks to its low cytotoxicity, the prepared TPIP-FONs hold significant potential for use as an antibacterial agent in vivo. Furthermore, when considering its utilization in bacterial imaging and antibacterial treatments, this material represents an innovative approach to constructing next-generation theranostic materials for antibacterial applications and bacterial treatment (Gao *et al.,* 2018). Hence, this type of nanomaterial holds a promising influence on the future development of self-assembled small molecules, not only for antibacterial uses but also across various other areas within the biomedical field.

Despite the excellent chemical and physical properties demonstrated by organic-based nanomaterials in combating MDR bacteria, these organic-based materials are often regarded as less stable, particularly when subjected to high temperatures. As a result, challenges may arise in designing products or materials that possess stability and can endure harsh process conditions (Beyth *et al.,* 2015). Therefore, inorganic-based materials have emerged as alternative options in the treatment of infections caused by MDR bacteria.

3.0 INORGANIC-BASED NANOMATERIALS

3.1 Metal/Metal Oxide Nanomaterials

Inorganic-based nanomaterials have found extensive application in the biomedical field, particularly in cancer treatment, immunotherapy, and bacterial infections, owing to their strong biocompatibility, low toxicity, and ease of modification (Chaudhary *et al.,* 2016). In the application of antibacterial materials, metal, or metal oxide NPs are among the extensively utilized inorganic-based nanomaterials (Loomba and Scarabelli, 2014). Metallic NPs such as gold (Au) and silver (Ag), as well as metal oxides such as zinc oxide (ZnO), titanium dioxide (TiO_2), and iron oxide (Fe_3O_4), have been extensively researched and developed owing to their excellent antibacterial properties (Beyth *et al.,* 2022).

The silver nanoparticles (AgNPs) demonstrate a broad spectrum of antimicrobial properties. These properties arise from their capacity to infiltrate bacterial cell walls, thereby altering cell membrane structures and ultimately resulting in cell death (Beyth *et al.,* 2022). Several works also have demonstrated that the modification of AgNPs with antibiotics such as amoxicillin, benzylpenicillin, clindamycin, erythromycin, and vancomycin create a synergic effect in treating MDR infections caused by bacteria such as *Staphylococcus aureus* and *Escherichia coli* (Shahverdi *et al.,* 2007). In order to possess effective antibacterial properties, several factors need to be considered and addressed prior to rendering them suitable for applications in medical and healthcare products. These applications could involve treating infections or efficiently preventing them. Limitations such as silver resistance in certain bacteria (e.g., *Acinetobacter baumanii*) and conditions like argyria, which result from the deposition of silver into the skin, must be addressed (Prasher *et al.,* 2018). In addition, the toxic properties exhibited by AgNPs towards fibroblasts, hepatocytes, osteoblasts, or bone marrow cells are among the primary concerns that need to be addressed by researchers (Prasher *et al.,* 2018).

Similarly, gold nanoparticles (AuNPs) have also attracted significant attention, primarily owing to their biocompatibility and surface modification (Okkeh *et al.,* 2021). One notably significant feature of AuNPs is their localized surface plasmon resonance (LSPR), which offers advantages in numerous applications in nanotechnology. The LSPR occurs when the electrons on the surface of metal NPs interact with electromagnetic radiation, resulting in the formation of LSPR. This interaction enables AuNPs to exhibit strong scattering spectra, thus demonstrating their advantage in various applications (Venditti, 2019). Antibacterial AuNPs are based on three approaches which are pristine antibacterial AuNPs, antibacterial photothermal therapy (APTT) based on AuNPs, and antibacterial photodynamic therapy (APDT) based on AuNPs (Okkeh *et al.,* 2021). Various studies have reported that AuNPs exhibit a range of functions and activities when interacting with bacteria, in order to overcome its resistance mechanisms. For example, Yang *et al.* (2017) demonstrated that AuNPs modified with β-lactam antibiotics, such as 6-aminopenicillanic acid (APA), have remarkable antibacterial properties against MDR gram-negative bacteria, such as

Escherichia coli and *Klebsiella pneumoniae*. The modification of AuNPs with APA in these studies also showed that this material can withstand bacteria and exhibits good biocompatibility (Yang *et al.,* 2017). While various AuNPs-based antibacterial materials show promise, a major challenge to be addressed before they can be fully commercialized is their toxicity. It is worth mentioning that the toxicity of AuNPs can result from a multifactorial process. For instance, the toxicity of AuNPs and their distribution throughout the body can be influenced by factors such as size, shape, concentration, surface modification, and various other variables (Okkeh *et al.,* 2021).

For example, although AuNPs have been classified as non-toxic, some studies have found that they can be toxic to humans. Particularly, AuNPs with a diameter of *ca.* 1.4 nm have been known to be toxic to human cells (Senut *et al.,* 2016). Meanwhile, the shape of AuNPs was also found to affect their toxicity. Studies by Steckiewicz *et al.* (2019) revealed that star-shaped AuNPs exhibit the highest cytotoxicity towards human cells. Additionally, in osteosarcoma cells, AuNPs in rod shape and star shape led to the upregulation of the Bax protein and downregulating Bcl-2 protein. The studies suggested that the shape of AuNPs determines how they penetrate the cell membrane, leading to ultrastructural changes. In terms of concentrations, one study found that AuNPs at a low concentration can induce modifications at the gene level after long periods of both chronic and non-chronic exposure (Falagan-Lotsch *et al.,* 2016). Finally, surface modifications have also been reported to influence the toxicity of AuNPs by reducing their effects. Studies by Ozcicek *et al.* (2021) showed that when AuNPs were functionalized with polyethyleneimine (PEI) and polyethylene glycol (PEG), their biocompatibility and biodistribution were improved. The studies demonstrated that the surface modifications of AuNPs with PEI or PEG reduce neuronal toxicity and increase cellular Au uptake, hence suggesting an ideal biomaterial for *in vitro* and *in vivo* applications. Based on the effects and parameters discussed above, it can be said that reaching specific conclusions or a consensus on the safety of AuNPs remains challenging. Additionally, while NPs like Ag and Au are favoured, their high production costs necessitate the exploration of other cost-effective inorganic antimicrobial agents (de Lucas-Gil *et al.,* 2019).

Besides metal NPs, metal oxide NPs such as ZnO, TiO_2 and Fe_3O_4 have also attracted global attention for the treatment of MDR bacteria. Among them, ZnO-NPs have been widely proposed as next-generation nano-antibiotics against microbes for the treatment of MDR infections. Various reports in the literature have shown that ZnO-NPs have high antimicrobial activity against MDR bacteria such as *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and the *M13 bacteriophage* (Jin and Jin, 2021). Physicochemical characterization of ZnO-NPs provides valuable insights into biological and biochemical responses to microorganisms, facilitating the prediction of antibacterial effects and toxicological effects (Czyżowska and Barbasz, 2022). For instance, several studies have reported the particle size-dependent antibacterial activity of ZnO-NPs, which demonstrates that the antibacterial performance is directly proportional to particle size (Xie *et al.,* 2011). It has been demonstrated that ZnO shows excellent antibacterial activity when the particle size is nano-sized. In this case, nano-sized ZnO interacts with the surface of bacteria or the bacterial core upon entering the cell, subsequently exhibiting distinct antibacterial mechanisms, as shown in Figure 4 (Sirelkhatim *et al.,* 2015). For example, a biosynthesized ZnO prepared by Ali *et al.* (2020) successfully reduced the formation of extracellular products such as pyocyanin, protease, and hemolysin in *Pseudomonas aeruginosa* ($p \leq 0.05$). The respective bacteria confer its pathogenesis and develop MDR via quorum sensing. Basically, *Pseudomonas aeruginosa*, an opportunistic pathogen, targets individuals with various severe medical conditions such as people with compromised immune systems and cancer patients as well as those with medical implants or individuals who have suffered burn (Andronescu *et al.,* 2012). Another study showed that ZnO-NPs and drug-conjugated NPs had no adverse effects on human cells. The combination of drugs with ZnO-NPs demonstrated significant antibacterial activity while causing minimal harm to human cells. These findings are highly significant and have the potential to serve as guidelines for designing new antibacterial formulations (Akbar *et al.,* 2021).

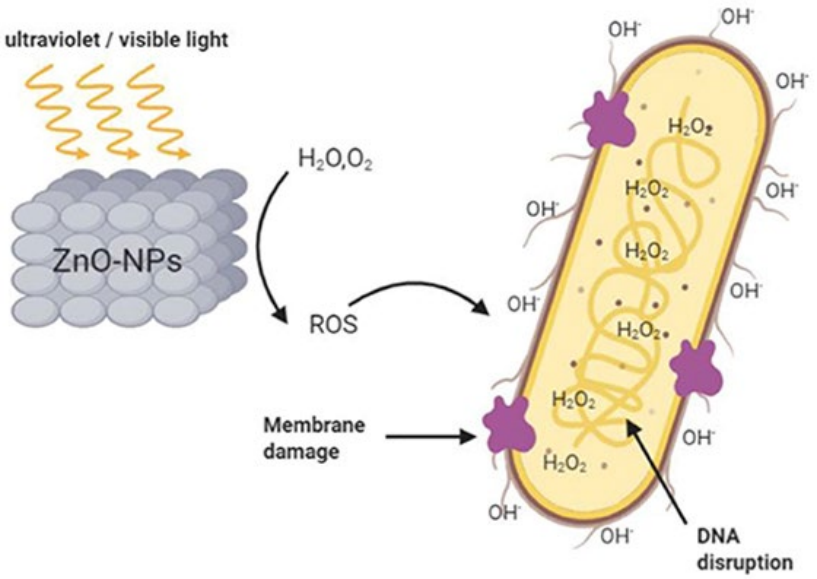


Figure 4 Mechanism of ROS production from ZnO-NPs and their bactericidal effect (Jiang *et al.,* 2020). This figure was reproduced from an open-access article published by Frontier Media S.A under Creative Commons Attribution license (CC BY).

The presence of defects in the structure of ZnO-NPs has been reported to enhance their antibacterial activity against MDR bacteria. For example, de Lucas-Gil *et al.* (2019) showed that the ZnO-NPs with a high crystal defect lead to the greater release of Zn^{2+} and enhanced surface activity. The defects, as revealed via Raman spectroscopy, showed that the significant contribution of 2LA mode was correlated with the defects in the crystallinity of ZnO-NPs. In addition, the decrease in the production of ROS also contributes to the improvement of the Zn^{2+} cations. Thus, it can be said that the high polarizability of crystal defects promotes electrostatic attraction between ZnO-NPs and the negatively charged bacterial membrane. This attraction, in turn, facilitates the penetration of Zn^{2+} and the generation of charge-free ROS (de Lucas-Gil *et al.*, 2019). Therefore, the synergistic effects of surface reactivity of Zn^{2+} and the presence of ROS contribute to the destruction of MDR bacteria. Hence, it can be concluded that the promising results with ZnO-NPs could pave the way for the development of inorganic antimicrobial agents to combat MDR bacteria.

Doping ZnO with metal ions has been shown to change the physiochemical properties of ZnO-NPs. Several works have demonstrated that doping or modifying with metal ions such as cobalt (Co), chromium (Cr), iron (Fe) and silver (Ag) can enhance its properties, making it suitable for various applications in photocatalysis, sensors, and even the biomedical field (Sharma *et al.,* 2022). Naskar *et al.* (2020) showed that doping ZnO-NPs with Ni element has improved the antibacterial performance of ZnO-NPs against the MDR strains of *Acinetobacter baumannii* and *Escherichia coli* (Naskar *et al.,* 2020). The modified Ni-ZnO produce seven to 16 times more ROS in *Escherichia coli* compared to that of unmodified ZnO. It can be said that the techniques used in the preparation of ZnO-NPs as reported above can serve as guidelines for the development of metal oxide-based nanomaterials for biomedical applications, particularly in designing nanoweapons to combat the ever-increasing public health threat of MDR bacteria.

However, several limitations and drawbacks associated with the use of ZnO-NPs in antibacterial applications must be considered. For example, several reports have indicated its toxicity, including hepatotoxicity, pulmonary toxicity, neurotoxicity, and immunotoxicity (Keerthana and Kumar, 2020). In addition, the high electron-hole recombination rate may limit the photodegradation of bacteria (Sirelkhatim *et al.,* 2015). This is attributed to the wide band gap of ZnO, which results in its selective absorption of UV light, causing the photocatalytic activity to occur exclusively within the UV region (Sirelkhatim *et al.,* 2015). Consequently, enhancing the efficiency of ZnO has emerged as a prominent research focus in the past few years.

Moreover, due to the high concentrations of zinc used as part of a human diet over several days, it may trigger resistance. Consequently, surviving intestinal bacteria can develop resistance not only to zinc but also to antibiotics, even if the animal is not in direct contact with antibiotics (Ciesinski *et al.,* 2018). Although doping can reduce the wide band gap energy of ZnO, not all elements are suitable for doping with ZnO to achieve a strong antibacterial effect, especially elements with larger ionic radii than Zn ions. This can be a disadvantage because the significant difference in ionic radii results in low dopant incorporation and may disrupt the pristine morphology of ZnO. For instance, a larger ionic radius can induce a more pronounced distortion of the crystal cell and increase spontaneous polarization, leading to the activation of ZnO piezoelectricity (Puspasari *et al.,* 2022). Therefore, transition metal elements have been favoured for modification with ZnO due to their similar ionic radius to that of Zn. In addition to noble metal elements, both Ag and Au are also considered by many researchers to be incorporated with ZnO to enhance its antibacterial properties.

Besides ZnO, metal oxide nanoparticles such as TiO_2 NPs have been also reported for application as antibacterial agents, owing to their unique chemical and physical properties. Their antibacterial activity can be significantly contributed by the decomposition of bacterial outer membranes by hydroxyl radical, which leads to peroxidation of phospholipids and, subsequently, cell death (Shah *et al.,* 2008). In a study demonstrated by Priyanka *et al.* (2016), the as-synthesized TiO_2 NPs showed good antibacterial activity during daylight against several MDR gram-positive and gram-negative bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Escherichia coli*. TiO_2 is an excellent photocatalyst that requires UV light to initiate the photocatalytic oxidation reaction and subsequently produce ROS, enabling the decomposition of organic compounds and extinguishing cellular activity. (Azam *et al.,* 2012). However, considering human safety, the application of TiO_2 NPs as a biomaterial is not favourable as they require UV light for activation, and this UV radiation can lead to DNA damage in cells and human tissues (Dizaj *et al.,* 2014).

Recently, Fe_3O_4 has been reported to have good antimicrobial activity against MDR bacteria, such as *Staphylococcus epidermidis* and *Acinetobacter baumannii*. Moreover, the as-prepared Fe_3O_4 NPs, as reported by Abdulsada *et al.* (2023), demonstrated good antimicrobial properties against both gram-positive and gram-negative bacteria. Similar to ZnO and TiO_2 NPs, the formation of ROS generated by the Fe_3O_4 NPs contributes to their bactericidal activity, along with the chemical reactions occurring between Fe_3O_4 and the bacterial membrane. The high efficiency of Fe_3O_4 as an antimicrobial agent can be attributed to its good biocompatibility and low toxicity, particularly to humans. These properties suggest Fe_3O_4 as the ideal candidate for use as an antibacterial agent against MDR bacteria in the future.

3.2 Carbon-based nanomaterials

In addition to metal and metal oxide-based nanomaterials, carbon-based materials with intrinsic broad-spectrum antimicrobial activity also provide a promising solution to address the issue of MDR bacteria. To date, several carbon-based materials such as graphene, carbon nanotubes (CNTs), and fullerene have been reported to demonstrate good antibacterial properties (Teixeira-Santos *et al.,* 2021; Hatta *et al.,* 2023). The antibacterial mechanisms of carbon-based materials are typically attributed to a combination of several physical and chemical properties. For example, the materials can act directly on the bacteria, such as by disrupting the membrane structure of peptidoglycan, or indirectly by inducing the production of ROS (Serrano-Aroca *et al.,* 2021). Other mechanisms include enzyme inactivation, sharp-edge insertion, and cell-wall synthesis inhibition, as shown in Figure 5 (Díez-Pascual, *et al.,* 2021).

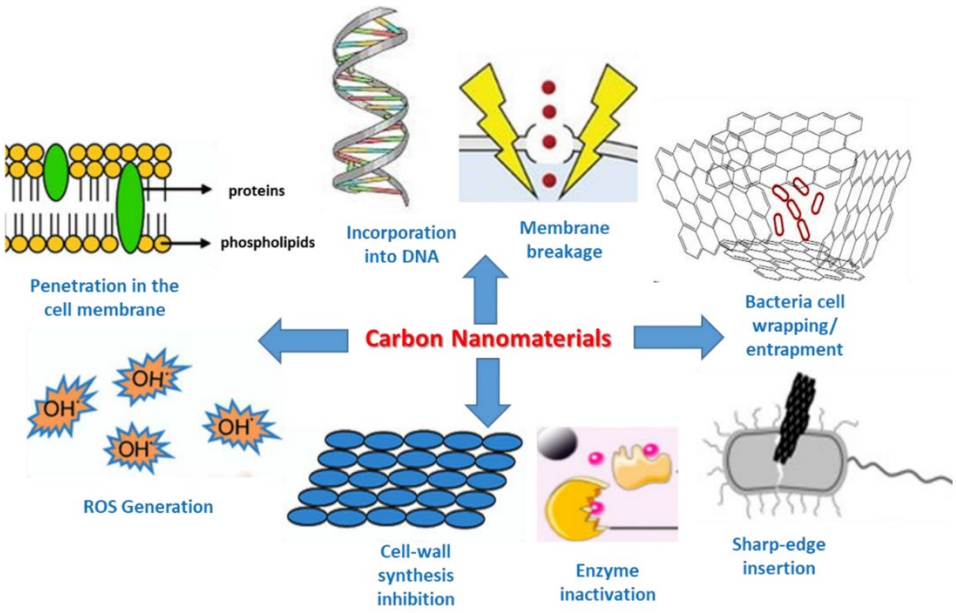


Figure 5 Antibacterial mechanism of carbon-based nanomaterials. This figure is reproduced from MDPI (Basel, Switzerland) under a Creative Commons Attribution licence 4.0 (CC BY 4.0).

In terms of graphene-based materials, it can physically destroy the membranes of bacteria by direct contact, due to its sharp edge. Moreover, the antibacterial activity of graphene can also be attributed to electron transfer as graphene can accept electrons from the membrane of bacteria and thus, significantly affect the structure of the bacterial membrane (Chen *et al.,* 2015). A previous report has shown that graphene can induce the degradation in both the inner and outer membranes of MDR bacteria *Escherichia coli* (Tu *et al.,* 2013). Furthermore, the *in-silico* studies showed that the pristine graphene can be inserted into the bacteria membranes and phospholipids due to the interactions between the pristine graphene and molecules of lipids. This destruction process provides a new mechanism for how the graphene materials work in antibacterial applications and their level of cytotoxicity (Tu *et al.,* 2013). Meanwhile, another study revealed that graphene demonstrated variable antibacterial activity towards both gram-positive and gram-negative bacteria, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It was found that the density of the edges of graphene significantly influences the antibacterial properties of graphene (Pham *et al.,* 2015). While several aforementioned studies have demonstrated the excellent antibacterial activity of pristine graphene, studies have shown that pristine graphene is not easily biodegradable. In addition, it was reported that pristine graphene demonstrated toxicity, especially graphene sheets with densely packed. Therefore, the amount of uptake of graphene-based materials in living organisms must be reduced (Ban *et al.,* 2023). Studies have also shown that graphene demonstrates toxicity in the epithelial cells and luminal macrophages, however, the reported level of toxicity was low (Van Den Broucke *et al.,* 2021).

Another graphene-based material, graphene oxide (GO) has been demonstrated to be a more efficient antimicrobial agent owing to the presence of functional groups such as carboxyl or hydroxyl, which facilitate the binding of GO with different molecules (Kumar et al., 2019). In the past few years, there have been many studies reporting the successful application of GO as an antibacterial agent against gram-negative and gram-positive bacteria. For example, a study by Nanda *et al.* (2016) revealed that the GO can easily penetrate the thin layer of peptidoglycan of the gram-negative *Escherichia coli* bacteria. On the other hand, another study claimed that the antibacterial activity of GO was more potent in gram-positive bacteria (*Staphylococcus aureus*), owing to its thick peptidoglycan layer (Ghanim *et al.,* 2018). Figure 6 shows the several types of antibacterial mechanisms of GO, which consist of disruption of the bacteria cell membrane (1), leakage of intracellular content (2), entrapment of bacteria known as wrapping effect (3) and oxidative stress. According to the review by Mohammed et al. (2020), five physical and chemical properties affect the antibacterial performance of graphene-based materials, such as the lateral size, numbers or layers, particle shape, surface modifications and agglomeration and dispersion (Table 3).

Despite several reports and works that have demonstrated the excellent antibacterial performance of graphene-based materials against MDR bacteria, there are several issues and challenges linked with these materials. For example, more evidence is required to fully understand the mechanisms of graphene-based materials in antibacterial activity and to correlate this activity with the innate immune system as potential future antibiotics for MDR bacteria (Mohammed *et al.,* 2020). Furthermore, safety concerns about these materials particularly in terms of their toxicity to living organisms must be addressed first before being commercialized. For instance, concerns such as how graphene-based materials will be accumulated inside the body must be thoroughly addressed. It was reported that graphene-based materials can accumulate in the lungs and liver. However, the long-term effects of this accumulation are still unknown (Zhang *et al.,* 2021).

Other challenges and limitations that remain include fully understanding the antibacterial mechanism behind the interaction of bacteria and graphene-based materials. Although various studies have reported the toxicity of graphene-based materials, there is still an argument about their effects on human and animal cells during practical applications. This could be attributed to inconsistencies in research findings and the lack of universally accepted criteria for assessing the biocompatibility and toxicity of the materials, which need to be addressed before turning into clinical practice (Kumar *et al.,* 2019). Moreover,

the majority of antibacterial studies involving graphene-based materials were conducted on *Escherichia coli* and *Staphylococcus aureus* bacteria. Therefore, it is crucial to investigate the materials with other MDR species in order to confirm their broad bactericidal range (Kumar *et al.,* 2019).

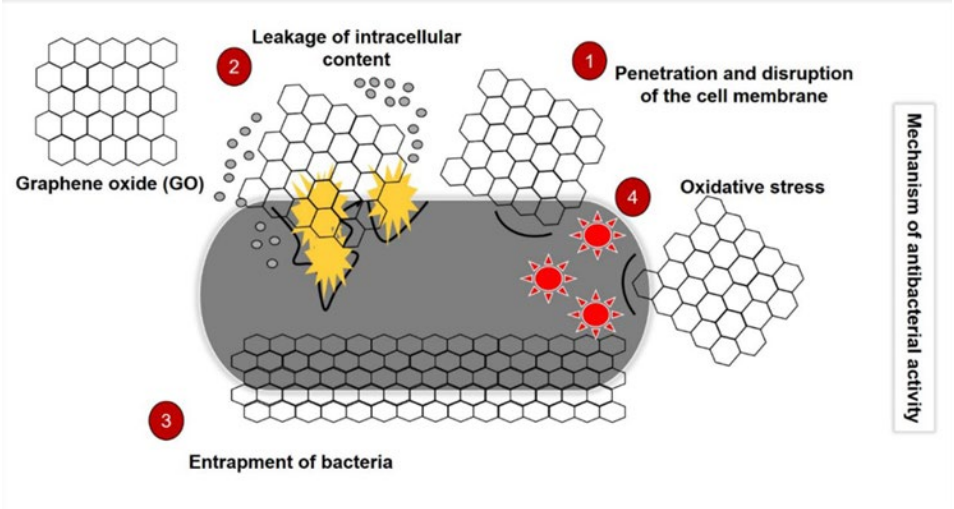


Figure 6 Four different mechanisms of antibacterial activity by GO. This figure was reproduced from an open-access article published by MDPI under a Creative Commons Attribution licence 4.0 (CC BY 4.0).

Table 3 Physical and chemical properties of Graphene-based materials.

Properties	Remarks
Lateral size	The adsorption, dispersion, and the edges of graphene are highly influenced by particle size, and these properties affect the interaction of graphene materials with bacteria.
Numbers or layer	The increased number of layers in graphene increases the thickness, weakening the 'nano-knife' effect, and subsequently decreasing dispersibility. Hence, this reduces contact between the bacteria and graphene materials.
Particle shape	The shapes of nanoparticles are crucial in determining their interaction with graphene-based materials during the translocation process across the lipid bilayer.
Surface modifications	The modification of the surface of graphene or edges plays a key role in preventing the particles from agglomerating and, thus, affecting their antibacterial properties.
Agglomeration and dispersion	The agglomeration of graphene-based materials reduce their dispersibility and adsorption capacity, which alter blade efficacy and consequently reduces their interaction with the microorganisms.

Another carbon-based material, carbon nanotubes (CNTs), has also been demonstrated to exhibit excellent antibacterial properties (Mohd Hatta *et al.,* 2023). The excellent antibacterial properties are due to their excellent physicochemical properties. For example, the strong carbon-to-carbon covalent bonds between atoms have been demonstrated to be an effective defence against multidrug-resistant bacteria (Huang *et al.,* 2011). In addition, multiwalled CNTs (MWCNTs) with a wide surface area and intrinsic toxicity of the surface would enable the harmful effect of nanoparticles (Freitas *et al.,* 2021), thus, making it the most researched CNT materials in the application of the biomedical field. In terms of the physical properties, the average diameter of CNTs, which is around 1 – 3 nm, significantly contributes to their antibacterial properties. This small diameter can induce damage within the bacterial cell membrane via cell-surface interactions (Saliev, 2019). To date, the application of CNTs-based materials as antibacterial agents against MDR infections is widely acknowledged and it is proposed to hold great promise as a next-generation antibacterial strategy that may replace the use of drugs (Xin *et al.,* 2019).

Several factors contribute to the antibacterial activity of CNTs. The nano-size, shape of CNTs, specific surface area, chemical composition on the surface, and functionalization have been the main parameters that can significantly affect their toxicity. Another factor, such as dispersity, has been shown to significantly affect the toxicity of bacterial cells. For example, it has been reported that the addition of functional groups to CNTs has resulted in enhanced dispersibility, leading to the inactivation of MDR bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*, with an activity of up to 90%. (Murugan and Vimala, 2011). Furthermore, the geometrical shape of CNTs was also shown to have a significant impact on their antimicrobial properties. In a study conducted by Kang *et al.* (2008), single-walled CNTs (SWCNTs) demonstrated better efficacy in destroying *Escherichia coli* compared to MWCNTs due to their more efficient penetration of bacterial cell walls. Moreover, the sharp diameter of SWCNTs allows them to penetrate bacterial cells more easily compared to MWCNTs (Smith

and Rodrigues, 2015). On the other hand, the ability of CNTs to generate ROS, such as oxygen radicals and hydroxyl radicals, is also responsible for destroying the bacteria (Jatoi *et al.,* 2020). The fatty acids in the cell will be oxidized by the reactive species, thus damaging cell permeability and subsequently affecting cell functions (Figure 7) (Patil *et al.,* 2021). Table 4 summarizes the recent applications of CNTs as an antibacterial agent in the treatment of MDR infections.

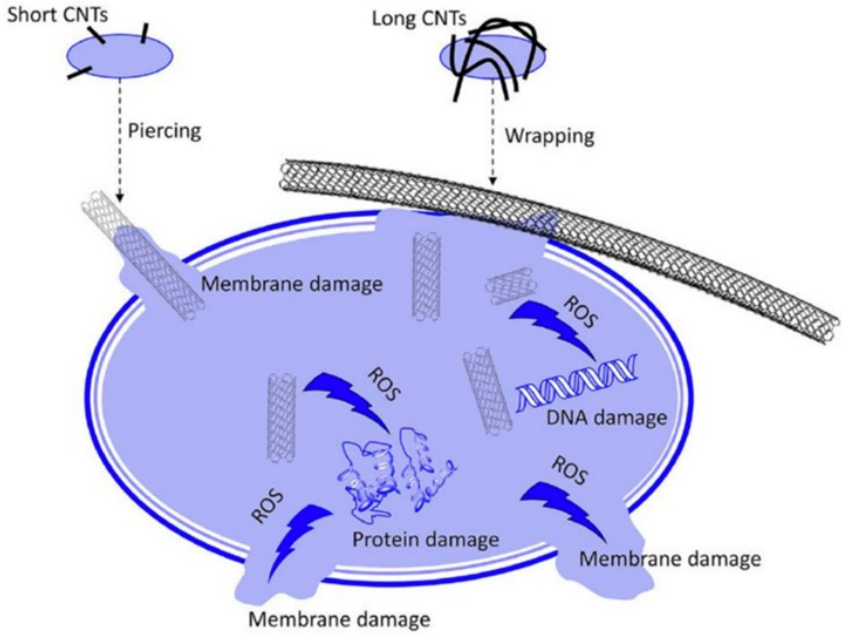


Figure 7 Illustration of CNTs' penetration into bacteria membrane using short and long CNTs. This figure was reproduced from an open-access article published by MDPI (Basel Switzerland) under a Creative Commons Attribution license 4.0 (CC BY 4.0).

Table 4 Recent report on the application of CNTs-based materials in the treatment of MDR infections.

CNTs	Microorganism assayed (MDR)	Activity	Reference
CNTs decorated with Hg	*Acinetobacter baumannii*	Inhibition of microbial growth.	Banihashemi *et al.* (2021)
SWCNTs-Ag-SiO_2	*Escherichia coli* and *Staphylococcus aureus*	High antibacterial activity due to improved dispersibility of CNTs.	Zhu *et al.* (2020)
Vertically aligned CNTs (VA-CNTs)	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	High reduction in cell viability (97 – 100%)	Schifano *et al.* (2023)
Unzipped CNT/PDA nanofibrous membrane	*Bacillus subtilis* and *Escherichia coli*	Excellent photothermal properties and high ROS-scavenging activity in the presence of NIR.	Patil *et al.* (2023)
SWCNTs functionalized with Methicillin	*MRSA*	Improved bacterial activity against MRSA compared to Methicillin alone.	Masoumeh *et al.* (2022)

Other carbon-based materials, such as carbon quantum dots (CQDs), graphene quantum dots (GQDs), and fullerene, are also considered potential therapeutic materials in the treatment of MDR bacteria. Previously, CQDs and GQDs have been reported as potential antiviral agents (Hatta *et al.,* 2023), and recently, a few reports have demonstrated their successful application as antibacterial agents. For example, CQDs functionalized with phosphorus have been shown to improve the antibacterial performance against common MDR bacteria such as *Escherichia coli* and *Staphylococcus aureus* (Chai *et al.,* 2022). Meanwhile, GQDs modified with titanium-based metal-organic frameworks (MOF) exhibited outstanding photocatalytic antibacterial performance against *Escherichia coli* and *Staphylococcus aureus*, with up to 75% and 93% activity, respectively (Yang *et al.,* 2023). Finally, fullerene-based materials have also been reported as effective antibacterial agents. Recent studies have shown that fullerene when combined with AgNPs, exhibited high antibacterial activity, as UV analysis revealed the destruction of the cells and DNA of *Staphylococcus aureus*. The antibacterial activity of Ag(I)–C60 was found to be up to 88% under light irradiation for 20 minutes, suggesting a significant amount of ROS production under light illumination (Pan *et al.,* 2023).

4.0 CONCLUSION

The nanomaterials have the potential to be the next-generation material in the fight against the MDR bacteria. However, studies on the safety aspects such as toxicity and biocompatibility of the materials intended for human consumption are highly needed

before implementing the material in clinical practice. In addition, the unique chemical and physical properties of various nanomaterials can have different effects on humans. Therefore, it is important to study their toxicity effects to reduce toxicity and improve bioavailability and stability. On the other hand, one of the challenges in using nanomaterials as antibacterial agents is the unclear mechanism of how bacteria will develop resistance to nanomaterials. Hence, studies on the mechanism of microbial resistance to nanomaterials should be conducted to avoid the issue of resistance linked to conventional antibiotics. Finally, we should explore the mechanism by which nanomaterials interact with biological systems to design and develop nanomaterials with favourable physical and chemical properties while ensuring they have no adverse health impacts.

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