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Review Article

Biogenic Nanomaterials: A Way Forward in Preventing Bacterial Infections

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Abstract: Antibiotic resistance puts a tremendous strain on the healthcare system. Bacteria such as *Staphylococcus aureus, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* that cause diseases like endocarditis, pneumonia, and Urinary tract infections have now become resistant to many previously used antibiotics. Antibiotic overuse must be reduced as it has become a public health threat paving the way to pandemics. Instead of creating new antibiotics, repurposing existing medicines that have faced resistance is one way forward. Plant-based antimicrobials have been explored as antibiotics to boost or augment the capability of existing antibiotics. It has been proposed that conjugates of plant-based products and antibiotics have increased activity and that the conjugated groups could help circumvent the beta-lactam antibiotic resistance mechanisms. Antibiotics have been combined with plant-based substances like Berberine, and a considerable synergy has been reported among them. Nanomaterials also promise a powerful environment-friendly strategy for weaponizing antibiotics with plant compounds. Nanoparticles could attach with many biological molecules such as DNA, enzymes, ribosomes, and lysosomes, further affecting the permeability of the cell membrane. The interaction of nanoparticles with many biological targets makes it hard for bacteria to develop resistance against them. Low molecular weight nanomaterial based on antibiotics could be very effective against multidrug-resistant gram-negative pathogens. Our study aims to analyze the progress done at the front of nanomaterials and nano-antibiotics against infectious diseases.

Keywords: Biogenic nanomaterials, Multi-drug resistant microorganisms, Metallic nanoparticles, Nanoparticles-biomolecule conjugate, Lipid nanoparticles

1. INTRODUCTION

The evolution of bacteria to acquire resistance to antibiotics dates back to the time when humans were trying to produce antibiotics at a large scale [1]. The reason behind the early and continuing evolutionary mechanisms of resistance includes the struggle of bacterial strains for resources, including the natural production of secondary metabolites, which are analogous to antibiotics used today as therapeutic agents [1]. However, most types of currently used antibiotics were revealed in 1940-1960, known as the golden era of antibiotics. At that time, it was believed that it would control the rate of infectious diseases [2]. Unfortunately, worldwide antibiotic resistance increased with time due to selection pressure, overpopulation, increased use of antibiotics in hospitals, wildlife spread, enhanced global migration, and poor sewage removal systems [3]. In the past few decades, many pandemics have occurred; the most recent one among them is COVID-19, which affected millions of lives. It is believed that COVID-19 worsened the global problem of antimicrobial resistance (AMR). The mortality rate is approximated to be 700,000 deaths per year due to unsuccessful antibiotic treatment,

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and it is expected to reach 10 million by 2050 [4]. Due to the rapid increase of multidrug resistance (MDR) bacteria, new therapeutic strategies are required to control the rate of infectious diseases because no new class of effective antibiotics against Gram-negative bacteria have been discovered in more than half a century, and only ~40 new antibiotics are in pre-clinical testing. Now it has become necessary to adopt new treatment strategies to halt the mechanism of resistance [5].

The surge of nanotechnology gives new hope for reducing the problem of antibiotic resistance. It has been reported in various laboratory-based studies that nanoparticles and antibiotics can synergistically act against pathogens. Various strains of bacteria are reported to be succumbed to nanoparticle stress and become susceptible to drugs [6]. Recent reports showed that by making conjugation of nanoparticles and antibiotics alleviates their toxicity to human cells and is also found to be effective at low dosages with enhanced bactericidal properties. Nanoparticles also repair the ability of antibiotics to destroy resistant bacteria. Nanoparticles when bound with antibiotics, enhances their bioavailability and facilitate their interaction with bacteria.

Similarly, nanoparticles combined with biomolecules possessing antimicrobial properties, such as antimicrobial peptides and essential oils are highly effective against resistant bacteria [7]. Nanoparticles previously produced by physical and chemical methods have limited use due to their toxicity to human cells. Now the most suitable method has been adopted, which is known as green synthesis because it is safe, non-toxic, and inexpensive. In nanobiotechnology, several biological systems, such as biomolecules, bacteria, fungi, yeasts, and plants, serve as ideal nano factories [8]. In the synthesis of nanoparticles plant metabolites, for instance, polyphenols have shown significant results because of their therapeutic value [9, 10]. The nanoparticles synthesized from plants are gold, zinc, magnesium, copper, silver, titanium, alginate, etc. Silver-based nanoparticles are more significant and show antimicrobial activity against bacteria, fungi, or protozoan pathogens [11]. A study revealed that silver nanoparticles conjugated with various drugs, such as ampicillin, streptomycin, gentamycin, and tetracycline, increase their stability and functionality and enhance antimicrobial potential against several resistant strains of bacteria *Escherichia coli, Staphylococcus aureus,* and *Staphylococcus pneumonia* [12]. Compared to chemically synthesized nanoparticles, plant-based nanoparticles show a better antibacterial effect, especially against multidrug-resistant organisms (MDROs), both individually and in synergy with current or conventional antibiotics [13]. Thus, this review focuses on applying green synthesized nanoparticles to combat antibiotic resistance to tackle current infections and prevent the emergence of new outbreaks.

2. BURDEN OF ANTIMICROBIAL RESISTANCE

Since the first use of antimicrobials, the burden of bacterial resistance has grown steadily and rapidly during the past ten years. Before the discovery of antibiotics, antibiotic-resistant genes were present in a few numbers. Still, the overuse/misuse of antibiotics and exposure to antibiotics with their companions, humans, animals, food, and environment led to antimicrobial resistance [14]. Antimicrobial-resistant is a global concern because it causes a burden on the healthcare and economic sectors, mostly because it limits the treatment options, increases the risk of failure of available therapies, increases the time of hospitalization, cost of treatment, and unrecognized outcomes such as increased mortality and morbidity [15]. Antimicrobial resistance is increasing rapidly, and AMR is expected to kill 10 million people annually by 2050. Murray *et al*. [16] estimated the resistance of strains of *E. coli* and *Klebsiella pneumoniae*. He concluded that both strains have become resistant to third-generation cephalosporins and carbapenems in almost 193 countries, which is alarming [16].

Similarly, *Salmonella spp*. is estimated to cause 3 billion human infections annually. Ciprofloxacin is the first-line drug to treat patients suffering from typhoidal salmonellae. Still, there is an increase in bacterial strains against ciprofloxacin, which causes a fear of treatment failure and necessitates the need for new antibiotics [17]. Some other pathogens due to their multi-drug resistant properties have shown to escape clinical treatments: *Campylobacter, Salmonella, Enterobacteriacea,* Methicillin-resistant *Staphylococcus aureus* (MRSA),

Vancomycin-resistant Enterococci (VRE), and New Delhi Metallo-β-lactamase (NDM)-1 [18]. To reduce the current burden of AMR, it is important to know the pathogen-drug combinations contributing to the burden of bacterial AMR and its global trend. Development of AMR is a continuous process and if it is not treated, many pathogenic bacteria could become much more lethal in the future than they are now [18].

3. MECHANISM OF ANTIBIOTIC RESISTANCE

AMR is an inescapable evolutionary outcome of all organisms evolving genetic alterations to evade deadly selection pressure. As long as antibacterial medications are employed against bacteria, they will evolve and adapt resistance methods (Figure 1) [19]. The lack of effective antibiotics in development contributes to the rise of resistance to existing antibacterial agents. In addition to acquiring antibiotic resistance by horizontal gene transfer and mutation in a chromosomal gene, bacteria can also possess intrinsic resistance to certain antibiotics [20]. For instance, triclosan has an extraordinary antibacterial effect against the diverse class of bacteria, which is why innate resistance in an individual species occurs when the bacteria are not susceptible to an antibiotic [21]. Although active efflux has initially been thought to explain this, it fails to inhibit the growth of Gram-negative *Pseudomonas* due to the occurrence of the fabl gene, which produces an enzyme named enoyl-ACP reductase which targets triclosan in susceptible strains [22].

Bacteria can acquire or evolve antibiotic resistance in addition to their intrinsic resistance. Four mechanisms are responsible for causing this effect: they either 1) reduce the intracellular concentration of the antibiotic due to inadequate bacterial penetration; 2) activate antibiotic efflux, [23]; 3) modify the target of the antibiotic via genetic mutation or post-translationally, and/or 4) inactivate the antibiotic by hydrolyzing or modifying it [24].

Gram-negative bacteria show impermeability to certain drugs because their external membrane, which contains a lipopolysaccharide layer, generates a permeability barrier [25]. A good example of the effectiveness of the bacterial outer membrane can be seen from the fact that glycopeptide antibiotics, such as vancomycin, remain ineffective against Gram-negative bacteria due to a lack of penetration through the outer membrane [26]. Changes in the outer membrane's permeability significantly impact hydrophilic compounds, such as β-lactams, tetracyclines, and some fluoroquinolones [27]. Another way in which bacteria colonize is through the production of biofilms. Polysaccharides, proteins, and DNA make up the biofilm matrix, which makes it difficult for antimicrobial agents to enter the bacterium and serves as protection [28].

The expression of the efflux pump is one of the intrinsic resistance strategies possessed by Gram-negative bacteria. Most of the drugs expel out of the bacterial cell through these pumps [29]. Most bacteria have a variety of efflux pumps. The five major classes of efflux pumps, grouped as a result of their structure and energy source, are the ATP-binding cassette family, small multidrug resistance family, large facilitator superfamily, and multidrug and toxic compound extrusion resistance-nodulation-cell division [30]. Except for resistance-nodulation-cell division, which has multiple pumps that cause the efflux of substrates over the cell envelope, all others possess single pumps that expel drugs through the cytoplasmic membrane.

Bacteria may produce enzymes capable of attaching different chemical groups to medicines [31]. This inhibits the antibiotic's ability to attach to its target in the bacteria. To inactivate a drug, chemical group transfer is the most effective method that involves the transfer of acetyl, adenyl, and phosphoryl groups [32]. Acetylation is the most used method, and it is thought to be used with chloramphenicol, fluoroquinolones, aminoglycosides, and streptogramins. In contrast, adenylation is thought to be involved in targeting aminoglycosides. Aminoglycoside modifying enzymes covalently change an aminoglycoside molecule's amino groups or hydroxyl, rendering it inactive. It is one of the most reported instances of antibiotic resistance [32].

β-lactam drugs including cephalosporins and penicillin, are extensively used, antibacterial agents. All members of this pharmaceutical category have a β-lactam loop with four sides, which serves as

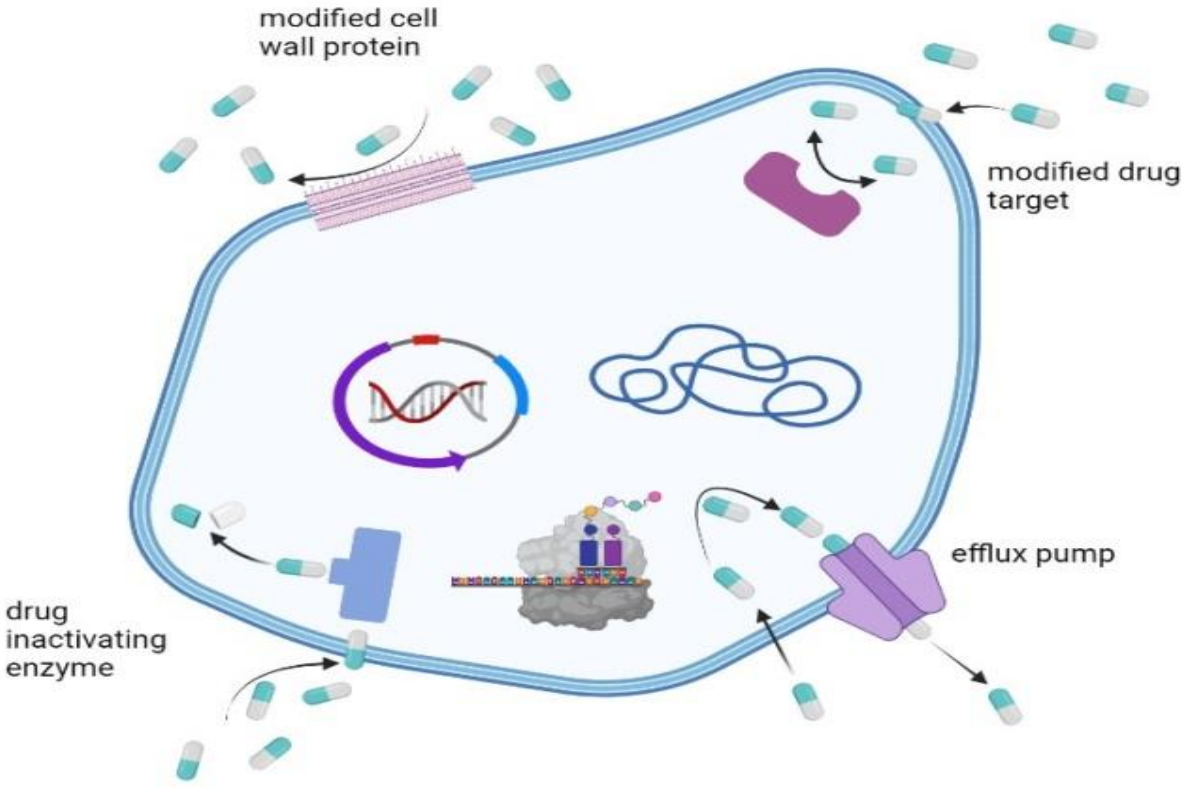

Fig. 1. Diagrammatic representation of antibiotic-resistant mechanisms adopted by bacteria

its primary structural component. The primary mechanism of β-lactam resistance, the β -lactam loop, is destroyed by the action of β -lactamases. The hydrolysis of β-lactam ring formation by the β -lactamases prevents it from attaching to penicillin-binding proteins (PBP) [33].

One typical pathway for the development of antibiotic resistance is the modification of the drug's target [34]. One of the mechanisms of resistance to β-lactam antibiotics is causing changes in the organization and/or quantity of PBPs. Changes in the number of PBPs alter the quantity of medication that can bind to the target [35]. A structural change, such as activating the mecA gene in S. aureus, will limit or prohibit drug binding. In response to drugs that block nucleic acid syntheses, such as fluoroquinolones, DNA gyrase, and topoisomerase IV may become resistant due to changes in their proteins [36]. Gyrase and topoisomerase undergo structural changes due to these alterations, which decreases or eliminates the drug's ability to bind to these proteins.

4. POTENTIAL OF RESISTANT PATHOGENS TO CAUSE A PANDEMIC

As we live in the era of antibiotics, the continuous use of antimicrobials increases the selection pressure on bacterial species to evolve and become untreatable, creating a hopeless situation [37]. Before the emergence of SARS-CoV-2, a "silent pandemic" was going on for more than three decades that caused more than 50,000 deaths each year in 2019. This resulted from multidrug-resistant (MDR) bacteria such as cephalosporin-resistant *K. pneumoniae, E. coli,* and carbapenem-resistant *Acinetobacter baumannii.* Studies have also shown that before the SARS-CoV-2 pandemic, the cases of pneumonia caused by antimicrobial-resistant Gram-negative bacteria were on the rise in many parts of the world [38]. Compared to other gram-negative bacteria, the *Acinetobacter* species acquire resistance much faster and become resistant to even new antimicrobials [39]. The most well-known infection caused by *Acinetobacter* species is ventilator-associated pneumonia. Due to their ability to survive in the hospital environment,

they also have the potential to cause nosocomial outbreaks [39].

Similarly, *Mycobacterium tuberculosis* was one of the most dangerous and dreaded bacterial illnesses before the advent of antibiotics. Thus, it can potentially result in a global epidemic [40]. According to WHO, 500,000 multidrug-resistant TB (MDR-TB) cases have been approximated amongst which 186,772 were only able to be diagnosed. Only 57 % of them were cured [41]. The use of antimicrobials increased during the COVID-19 pandemic. During the treatment of COVID-19, antibiotics are overprescribed, which increases the chances of secondary infections. Polly *et al*. [42] reported an increase in the incidence of Carbapenem-resistant *A. baumannii* (CRAB) and Methicillin-resistant *Staphylococcus aureus* (MRSA) infection both in ICUs and non-ICUs units. We are also facing antimicrobial resistance crises due to the failure of existing treatment strategies and the lack of new drugs. If the situation remains the same and we do not use available antimicrobials wisely, there are chances that we will return to the pre-antibiotic era of incurable diseases [43].

5. CHALLENGES IN TRADITIONAL ANTIBIOTICS DISCOVERY

Over the past 25 years, the challenges to discovering antibacterial drugs have kept the output of novel antibacterial drug classes at extraordinarily low levels. Resistance to the antibiotics can be caused by the failure of the drug to reach its target, either inactivated or altered, or by acquiring a target bypass system. For instance, the cell membranes of some microbial species are impermeable and prevent drug influx. In contrast, others produce enzymes that reside within or near the cell surface and inactivate the incoming drug.

The most important challenge to novel antibiotic agents is their development and marketing approval. Although they have the potential to address the deficiencies of existing classes of antibiotics and are vitally important to address the ever-increasing problem of bacterial resistance, a marked innovation gap in antibiotic development has been shown by examining the current industry pipeline over the past 20 years. There has been a decline in new antibiotic approvals, while the existing antibiotics are losing effectiveness more rapidly than they can be replaced. Difficulties associated with novel antibacterial discoveries and the reality that innovation of most new targets or chemical space approaches needs longer development. This indicates that novel solutions like nanoparticles have the greatest potential against bacterial resistance. Therefore, we must continue to apply what we have learned over the past decades and continue to strive to develop novel technologies against bacterial resistance [44, 45].

6. POTENTIAL OF NANOMATERIALS AS AN ALTERNATIVE TO TRADITIONAL ANTIBIOTICS

The discouraging financial incentives for commercial development result from the lack of antibiotics in the clinical pipeline. The widespread emergence of highly resistant strains could lead to a precarious situation and threaten the health system's viability, as seen with the current COVID-19 crisis. In the meanwhile, potential has been shown by several nano-antibiotics as alternatives to antimicrobial approaches [46].

Nanoparticles have been reported as a promising alternative to antibacterial agents in recent years. They possess several biomedical applications, such as antibacterial activity, applicability in tissue engineering, drug and gene delivery, and imaging. Furthermore, a possible relationship between the morphological characteristics of nanomaterials and the magnitude of their antibacterial potential has been reported by nanomaterial research. During in vitro studies, nanomaterials have been proven to demonstrate strong activity against several bacterial strains. These nanomaterials have also been used as a vehicle for drug delivery, pharmaceuticals, and antibodies [47, 48].

In nanotechnology, recent advances open new avenues to overcome the challenges by killing germs in bacterial infections without antibiotics. Advanced nanomaterials have presented antibiotic-free antibacterial strategies. Based on their mode of action, nanomaterials are classified as drug delivery agents for the delivery of natural compounds possessing antibacterial activity. Conventional antibiotics have the capability to potentially prevent the formation of new cell walls or chemically digest

the membranes of bacteria. However, nanomaterials can directly destroy the bacterial cell membrane through direct contact with bacterial cells. Regardless of the gram strain of bacteria (either gram-negative or gram-positive), the mechanism of antibacterial activity of nanoparticles lies in the physical harm to the bacterial cell membrane. Thus, nanomaterials have broad-spectrum antibacterial applications with little chance of resistance development. The other strategy of nanoparticles killing bacteria is generating toxic components, like reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage the intracellular proteins or genes by inducing lipid peroxidation of the bacterial cell membrane. To develop antibacterial nanomaterials that also include metal oxide nanoparticles efficiently generate ROS, tremendous efforts have been devoted [49].

Different nanoparticles are effective against resistant bacteria, and their antibacterial activities are size and shape-dependent. Nanoparticles like silver, gold, and Iron have shown a much more pronounced antimicrobial activity. Iron oxide nanoparticles show a repressive effect against bacteria like *S. aureus, S. enterica, P. mirabilis,* and *E. coli.* Similarly, zinc oxide nanoparticles have been reported to disrupt the cell wall of R. solanacearum indicating their good antibacterial potential. It is regarded as safe possessing light-activated oxidizing and catalytic effects. ZnO is found to be very effective when it comes down to the size range of nanometers. Due to its small size, ZnO becomes further effective in interacting with bacterial cells by penetrating them [50].

Furthermore, AgNPs have also been extensively tested against resistant pathogenic bacteria. It has been suggested that bacterial cells, when exposed to AgNPs, lose their DNA replication ability. The cell cycle halts at the G2/M phase due to DNA damage. Oxidative stress affects the cell, which is caused by the occurrence of ROS and inhibition of ATP synthesis. The release of silver ions from the AgNPs is another reason for bacterial cell death after exposure to these nanoparticles. It is believed that after penetration, the releasing atomic Ag0 and ionic Ag+ clusters inactivate the bacterial enzymes and cause cell death by producing hydrogen peroxide and other free radicals [51].

7. IMPORTANT PROPERTIES OF NANOMATERIALS THAT MAKE THEM EFFECTIVE

Nanoparticles exhibit interesting properties compared to their metallic counterparts. This means that the designed elements of nanomaterials play the most important role in making them effective [52]. Consequently, nanomaterials find too many applications in catalysis, diagnosis, electronics, sensors, and therapeutics. These properties include crystallinity, excellent stability, smaller size, surface plasmon resonance effect, unique shapes, and their higher surface-to-volume ratio [53]. These properties confer nanoparticles the extraordinary ability to be strongly antibacterial, antifungal, larvicidal, and antiprotozoal. More specifically, the unique size, crystal structure, and smaller size make nanoparticles superior to existing antibiotics which can ultimately lead to a reduced burden of antibiotic resistance [54].

Further, the nanoparticles have manageable morphology and good size dispersity [55]. Anisotropic is the main property of nanoparticles, which means their various crystal facets possess a different form of reactivity [53]. Metal nanoparticles, especially, make use of their stability, high surface-to-volume ratio, and improved electronic and optical properties to be more effective against pathogenic bacteria [56]. The optical properties of metallic salts are changed by changing the surface chemistry when converted to nanoform. The remarkable change in these properties mentioned above and the potential of customization of these properties have led nanoparticles to become one of the best avenues for fighting antibiotic resistance [57-59].

8. FROM TRADITIONAL NANOTECHNOLOGY TO NANOBIOTECHNOLOGY

Nanotechnology has rapidly developed as a significant field with applications in almost every aspect of life. The concept of the nanometer was first proposed by Richard Zsigmondy, the 1925 Nobel Prize Laureate in chemistry. Furthermore, the advancement to modern nanotechnology was led by Richard Feynman, the 1965 Nobel Prize Laureate in physics. He presented the concept

of employing matter at the atomic level. In its simplest form, nanotechnology is referred to the construction, design, and control of materials and particles with sizes less than 100 nm. Traditionally it gained the major attention of engineers and physical scientists because nanomaterials were employed in constructing computer chips and electronic devices. Today, progress in nanotechnology research has enabled scientists to develop techniques and systems for biological and medical research and applications that are referred to as nanobiotechnology [60, 61]. Nanobiotechnology enables to manipulate materials at a molecular and atomic level to synthesize ultra-small structures of biological importance [62]. It generally covers the applications of nanotechnology in rapid diagnosis and real-time monitoring, regenerative medicines, bioimaging techniques, directed and precise delivery of therapeutic agents, accurate therapy, and vaccine development [63].

In disease diagnosis and therapeutics, understanding the disease at a molecular level and then designing therapies accordingly using tools with such small dimensions is an ideal approach. These tools can be nanomaterials such as nanoparticles, nanoprobes, nanoconjugates, and nanocomposites [62]. The use of nanobiotechnological approaches can efficiently solve the problem of antibiotic resistance by fighting resistant bacteria. Various kinds of nanoparticles can be synthesized through biological means by using plant or microbial extract as a green media, where various biomolecules can act as reducing and capping agents. As a result, nanoparticles with high stability and increased dispersity are synthesized [50]. These nanoparticles can get attached to the bacterial cell wall and rupture it [64], destroy the cell organelles that disturb biochemical pathways [65], or generate reactive oxygen species that damage proteins and DNA [66].

Overall, nanoparticles possess excellent antibacterial properties as they can efficiently interact with bacteria, target multiple sites and pathways, and ultimately leads to bacterial cell death. Nanoparticles efficiently bind with biomolecules and form nanoconjugates with many antibacterial applications. Nanoparticles conjugated with nucleic acid aptamers specific to pathogen help in its rapid detection in the sample [67]. The combined application of antibiotics and nanoparticle conjugate potentially reduces the toxicity of both components as it reduces their amount and doses. It also restores the antibacterial property of antibiotics to which bacteria have developed resistance by increasing their absorption and bioavailability [7].

Nanomaterials also perform a significant role in the formation of vaccines with the ability to surpass mutations, potentially preventing the emergence of new outbreaks. Nanoparticles that mimic antigens, safely carry them, and deliver them to the targeted region in a controlled manner have extensively contributed to the field of vaccine development [68]. Conclusively, nanobiotechnology has enlightened new ways of fighting microbial diseases with more specificity and accuracy.

9. GREEN METALLIC NANOPARTICLES AGAINST PATHOGENIC BACTERIA

With the advancement of nanotechnology in the area of medicine and its use in various applications, it is not surprising to observe its role in managing the antibiotic resistance problem [69]. Embedded in the framework of green nanotechnology, developing new methods for synthesizing nanoparticles is extensively important [70]. Various methods (chemical, physical and biological), have been studied and reported to fabricate and synthesize nanoparticles with the required morphological characteristics, and functionalities [71]. It is urgent to develop better approaches to speed up the introduction of antimicrobial materials using green nanotechnology [72]. Nanoparticles can be synthesized through biological methods by self-assembling them into nanosized particles. They can efficiently interact with bacteria and destroy them in several ways (as shown in Figure 2). Green-synthesized nanoparticles are applicable in electronics, biological markers, and antimicrobials and possess the advantages of being safer, reproducible, and cheap, which can boost chemical reactions [73].

9.1 Silver Nanoparticles

Silver nanoparticles (AgNPs) are the most popular type due to their antimicrobial properties. AgNPs are versatile [74], and have been used in antimicrobial

gel formulations, AgNPs-aided dressings for wound healing [75], orthopedic operations [76], medical catheters [77], blood-contacting implants [78], endodontic filling materials [79], dental instruments [80] and coating of contact lenses [81]. AgNPs have many applications in products like building materials, antimicrobial coating, textiles, wound dressing, medical products, cosmetics, food, and antibacterial properties [82]. AgNPs synthesized through a chemical approach produce toxic and dangerous compounds that can harm the environment, require high energy and high pressure, and are very costly [83]. Alternatively, the synthesis of AgNPs through biological methods is environment-friendly, evading the use of poisonous and hazardous compounds [84]. Biological methods used to produce AgNPs include the employment of bacteria, fungi, yeast, and plants. Their extracts contain enzymes, proteins, amino acids, carbohydrates, and vitamins, which help to synthesize stable and dispersed AgNPs. The biological method also controls the shape and size of nanoparticles [85].

Plant-based silver nanoparticles have unique chemical, physical and biological properties. The effectiveness of these AgNPs evaluated in vitro has been well documented in the literature [86-88]. Readily acting and broad-spectrum bactericidal activity of plant-based AgNPs on both gram-negative and gram-positive strains of bacteria have been reported [89]. Due to the effective bactericidal activity of AgNPs aided with a faster healing rate due to the microbe-free environment, its use in biomedical applications has increased over the past few years. Plant-based AgNPs -impregnated dressings that have low cytotoxicity or no cytotoxicity are considered very safe for patients with serious wounds [90]. The oxidative stress-generating ability of Ag^{+} released by AgNPs has been reported. With the release of Ag^{+}, ROS generate that ultimately causes stress at molecular and cellular levels resulting in increased calcium levels in intracellular space, destruction of membranes, phosphatidylserine exposure in the outer membrane, DNA breakdown, and activation of caspase-like protein [91].

The study of Patra and Baek [92] suggested that using plant and plant extract-reduced AgNPs could potentially inhibit the growth of well-known pathogenic bacteria. The similar negative effect of bioactive AgNPs on the growth of *S. aureus* and *P. aeruginosa* were reported [93]. Following the penetration of AgNPs across the cell membrane of bacteria, several crucial steps take place. The silver ions disturb and halt the DNA's replication process leading to cell death [94].

9.2 Zinc Nanoparticles

In recent years, the antibacterial properties of zinc oxide nanoparticles (ZnONPs) have drawn substantial attention globally, predominantly since nanotechnology has been used to synthesize materials in the nanometer range [95]. As a result of the increased specific surface area generated by the reduction in particle size, ZnONPs exhibit attractive antibacterial properties. Moreover, ZnO is a non-toxic compound with several light-activated oxidative and catalytic effects on various chemical and biological species, making it an appropriate material for bio applications [96]. The ZnONPs are considerably biocompatible, and their rate of electron transport is high, so they are appropriate for use as biological membranes and in any other biological application in which they may have a great deal of function [97]. ZnO nanoparticles exhibit significant antimicrobial activity against several pathogenic bacteria, including *P. aeruginosa, S. pyogenes, Klebsiella, B. subtilis, S. aureus, M. tuberculosis, E. coli,* and *P. mirabilis*. The great antibacterial properties of nanoparticles are reflected in their toxicity, which is also, unfortunately, a major drawback of nanoparticles.

In comparison to soluble Zn compounds such as Zinc chloride, ZnONPs have a better antimicrobial effect, as they possess more active targeting potential, and they are capable of generating ROS inside a cell membrane, thus disrupting the integrity of cell membranes as well through in the denaturation of proteins, lipids, and also DNA [98]. An investigation reported that ZnONPs were bactericidal and not bacteriostatic in their effect on *Campylobacter jejuni* bacterial culture since no recovery of bacterial cells was observed after the replacement of nutrients with ZnONPs [99]. The antibacterial effects of spherical ZnONPs (70 nm) were examined against E. coli. The ZnONPs were administered at concentrations ranging from 3 to 12 mM for 24 hours, and full growth suppression

was seen at the 12 mM concentration. The ZnO-NPs destroy proteins and lipids on the membrane of the bacterial cells, causing the membranes to be damaged, resulting in leakage of the intracellular contents of the cells, and causing the death of the bacteria [100].

The antibacterial activity of date palm extract-stabilized spherical ZnONP (97 nm) synthesized on cotton fabric was demonstrated by El-Naggar *et al*. [101]. Compared with uncapped ZnONP and date palm extract, capped ZnONP was found to have higher antibacterial activity against various bacterial species such as *P. aeruginosa, B. subtilis, S. aureus,* and *E. coli*. Moreover, these capped ZnONPs showed no detectable cytotoxicity against human cell lines even 72 hours after treatment.

9.3 Gold Nanoparticles

Gold nanoparticles (AuNPs) are effective against a variety of bacteria and are known for their high surface area, simplicity in functional group modification, and non-specific antibacterial action [102]. AuNPs have shown particularly beneficial antibacterial activity. They are nontoxic, highly biocompatible, and have very stable chemical properties [103]. AuNPs are unlikely to create resistance than conventional antibiotics because they target a range of components in bacteria, including DNA and proteins; thus, they make it harder for bacteria to develop defense mechanisms that can withstand all harm [104]. The antibacterial effects of AuNPs are mainly based on biofilm and cytoderm disruption, formation of ROS, and release of metal ions that cause bacterial cell destruction [105]. Phytochemicals of *Clitoria ternatea* leaves have been extracted in methanol to synthesize AuNPs [106]. In the anti-biofilm test against *P. aeruginosa*, the biofilm formation rate was repressed up to 94.4 % by using a concentration of 100 µg/mL. Zhou *et al*. [107] examined the antibacterial efficacy of AuNPs against *M. tuberculosis* and *E. coli,* two Gram-positive and Gram-negative pathogens, respectively. They concluded that Gram-positive M. tuberculosis and Gram-negative *E. coli* were significantly inhibited by AuNPs. Another research work by Boomi *et al.* [108] used the leaf extract of *Croton sparsiflorus* to synthesize AuNPs showing a good zone of inhibition against *S. epidermidis* and *E. coli* around 30 mm and 26 mm.

9.4 Iron Nanoparticles

Iron nanoparticles (FeONPs) possess strong activity against various harmful bacteria and can be utilized as a substitute for antibiotics, much like other metallic nanoparticles [109]. Biogenic FeONPs are proven to be effective antimicrobials. When compared to silver and gold nanoparticles, FeONPs are substantially more affordable [110]. In addition, they are favored because they are less harmful to individuals than other nanoparticles, particularly silver, which may be toxic to various cell types. The semi-crystalline biogenic iron oxide (FeONPs) nanoparticles were synthesized from Tridax procumbens ranging in size from 80 to 100 nm and showed bactericidal action against the Gram-negative bacteria *P. aeruginosa* [111]. FeNPs made from *Moringa oleifera* leaf extract in a different study showed antibacterial efficacy against *E. coli, P. aeruginosa, S. aureus, Pseudomonas multocida,* and *Salmonella typhi* [112]. Biocompatible FeO-NPs were produced from P. granatum peel extract that was highly effective against *P. aeruginosa* [113]. Very stable FeNPs were biologically synthesized to suppress certain harmful bacteria using *Lantana camara* plant extract. These nanoparticles efficiently inhibited *K. pneumoniae, P. aeruginosa*, and *S. aureus* [114].

10. GREEN SYNTHESIZED LIPID NANOPARTICLES AGAINST RESISTANT PATHOGENS

Lipid nanoparticles (LNPs) are unique particulate systems for effective drug delivery. It possesses the combined advantages of nano polymers, liposomes, and emulsions and overcomes their limitations in drug delivery applications [115]. The size of LNPs lies between 50-1000 nm after drug encapsulation, and they are made of biocompatible and biodegradable materials able to encapsulate and carry both hydrophilic and hydrophobic therapeutic molecules [116]. These nano-carriers are considered safe, nontoxic, biocompatible, and easy to produce [117]. Due to the high possibilities of their surface modification, they can encapsulate various molecules. The solid matrix (at room and human body temperature) enables them to gradually release the encapsulated active therapeutic

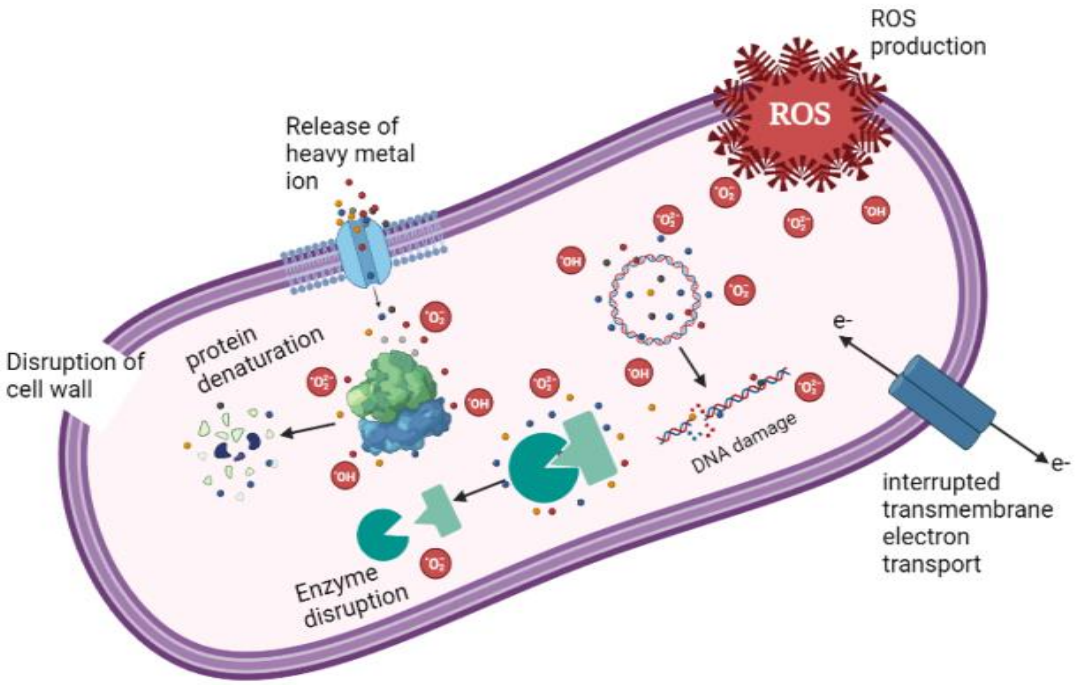

Fig. 2. Mechanisms through which nanoparticles interact with bacteria and disrupt them

ingredients in a controlled manner with enhanced intracellular permeability. The bioavailability of weakly soluble drugs can be enhanced with the use of such a particulate drug delivery system. Moreover, it can properly bio-distribute the drugs to the affected target areas [118, 119].

LNPs are green as their lipid component is derived from natural sources like purified triglycerides, glyceride compound mixtures, waxes, fatty acid esters, fatty alcohols, acylglycerols, and mixtures of acylglycerol esters. They are colloidal particles composed of a solid lipid matrix, surfactants (for stabilization), and active ingredients. Thus, the physiological lipid constituent in producing different LNPs makes it one of the primary drug delivery systems as it is biodegradable and biocompatible with minimum toxicity. LNPs were synthesized in the early 1990s in the search for the development of novel drug carriers. There are two major types of LNPs, namely solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLNs are modifications of liposomes, polymeric nanoparticles, and emulsions to overcome their limitations. At the same time, NLCs are the next generation of SLNs with few improvements, including high stability and increased drug loading capacity. They can be synthesized through various methods such as high-pressure homogenization, hot and cold homogenization, solvent emulsification, evaporation or diffusion, supercritical fluid (supercritical fluid extraction of emulsions (SFEE)), ultrasonication or high-speed homogenization, and spray drying [120]. The resultant LNPs can be applied as drug carriers in treating many diseases.
LNPs loaded with antibiotics are effective against bacteria because they can directly fuse with the cell wall of bacteria and gradually release the loaded therapeutic agent in response to bacteria. The LNPs and antibiotics act synergistically, thus increasing the cumulative antibacterial effect [121]. Rifampicin-loaded LNPs were tested in a skin-wounded mouse model to treat skin infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA). The study revealed that rifampicin-LNPs are more effective against MRSA than antibiotics alone [122]. Similarly, in a recent study, a complex of silver nanoparticles with clotrimazole was loaded on SLNs to test it against MRSA. This complex with SLNs showed the highest antibacterial activity and

was represented to be a good nano-antibiotic [123]. Another promising nano-antibiotic composed of vancomycin conjugated with linoleic acid loaded on SLNs has been developed against MRSA.

The resultant complex showed an enhanced antibacterial effect in *in vitro* antimicrobial tests with a minimum inhibitory concentration of 15.62 µg/ml [124]. Antibacterial oligonucleotide therapeutics such as transcription factor decoys (TFDs) have also emerged as molecules that can avoid AMR. However, their safe delivery to the target site is challenging as it requires protection from nucleases. LNPs have also been used to encapsulate and safely deliver these therapeutic oligonucleotides to fight *E. coli* infection. Its safe delivery to the bacteria was verified with high efficacy. Thus, LNPs are an effective delivery tool for novel antibacterial agents that can cross the barrier of AMR [125].

Furthermore, it has been identified that LNPs can be bactericidal without any loaded drug. A study revealed that NLCs could interact with and inhibit resistant H. pylori without affecting gut microbiota [126]. NLC can also deliver vaccines to generate a protective immune response [127]. They have also been employed to systematically deliver therapeutic small-interfering RNAs [128]. Overall, LNPs are an effective tool in the fight against antibiotic resistance as they can increase the potential of existing antibiotics and help the alternatives of antibiotics to be efficient. Such active drug carriers can competently treat recalcitrant bacterial infections and protect the world from new outbreaks.

11. NANOPARTICLES-BIOMOLECULE CONJUGATES AS AN IMPORTANT TOOL

Various nanoparticles have been recognized and employed as effective antibacterial agents against resistant bacterial strains. Due to their known therapeutic potential, more complex nanoparticles have been designed using different strategies. One of these is the conjugation of nanoparticles with biomolecules. Biomolecules can efficiently interact with nanoparticles and provide them with specificity. A stable and convenient conjugation between nanoparticles and biomolecules such as vaccines, drugs, peptides, proteins, and nucleotides can be achieved [129].

Antimicrobial peptides are desirable alternatives to antibiotics because of their broad-spectrum activity and with little chance of resistance development. However, they possess some limitations, such as poor enzymatic stability and permeability to the target site. It has been reported that AMPs conjugated with nanoparticles can form potent antibacterial agents with an enhanced antibacterial potential of both components with a synergistic effect that can effectively fight antibacterial resistance [130]. AgNPs are reported to effectively interact and conjugate with AMPs after tagging cysteine residue to the terminals of peptides. This conjugate is an active antibacterial agent against MDR *K. pneumoniae* [131]. AMPs esculentin-1a derived from frog skin conjugated with AuNPs showed 15 times higher antibacterial activity than peptide alone against free and sessile *P. aeruginosa.* The conjugate had no toxic effect on human keratinocytes. Thus, it suggested an attractive alternative for treating epithelial infection [132]. Polymyxin B (a cationic AMP having high potential against Gram-negative bacteria) linked with AgNPs was tested against MDR strains. The results showed that the conjugate lowered MIC value compared to the control. The SEM study revealed massive damage to the cell membrane and leakage of the cell contents resulting in cell death [133]. Nanomaterials conjugated lysozymes have also proved efficiently active against resistant bacteria (Gram-positive and Gram-negative). Lysozymes were immobilized on chitosan nanofibers which showed enhanced antibacterial activity by increasing the catalytic cleavage reaction of peptidoglycans in the bacterial cell membrane [49].

In the progress of vaccine development, nanoparticles can be loaded with diverse molecules including nucleic acids, peptides, and proteins, to form antigenic sources to be recognized by immune cells. Nano-formulations protect the antigens from enzymatic degradation and allow safe and controlled delivery to the target site [134]. Nanoparticles coated with outer membrane vesicles (OMVs) of bacteria have been successfully developed as effective immunogenic agents. When tested in mouse models, the outer membrane coating of *E. coli* on AuNPs revealed the activation of B and T-cell immunity along with the activation

of dendritic cells [135]. Moreover, Shigella OMVs loaded poly(anhydride) nanoparticles have revealed greater mucosal defense compared to free OMVs in a mouse model [136].

12. CURRENT CHALLENGES TO NANOBIOTECHNOLOGY

Nanobiotechnology has emerged as a revolution in medical science and can potentially overcome the shortcomings of conventional biomedical strategies. The applications of nanobiotechnology have already been discussed in the previous sections. The research community has been using nanobiotechnology to solve the global issue of antibiotic resistance. It is clear from the discussion in the previous sections that nanobiotechnology can be a potential strategy for preventing COVID-19, like pandemics. Although, like every other technology, nanobiotechnology also has certain challenges to face.

Despite all the benefits of using bio-nanotechnology as a biomedical strategy, there are still some challenges to overcome. The biggest possible limitation of using nanomaterials antimicrobials is their potential toxicity, which is unfortunately poorly understood [137]. Most inorganic nanomaterials are metallic [138]. Metallic nanomaterials are not only mutagenic but can also be potential endocrine disruptors, and therefore, using nanomaterials leads to human health compromise [139]. Adverse biological responses can be initiated by nanomaterials cause of their genotoxic and carcinogenic nature [140]. There is a high risk associated with the use of nanomaterials. They can be accumulated in human bodies and may have adverse effects [141]. This threat of possible toxicological outcomes is forcing biomedical researchers to find a way to minimize metallic nanomaterials' toxicity. Nanomaterials-induced toxicity can lead to serious health issues in immunocompromised patients. Therefore, a very high risk is associated with applying nanomaterials to human bodies [142]. To assess the toxic effects of nanomaterials, nanobiotechnology experts tend to promote the safe design and utilization of nanomaterials, act like aliens in the bloodstream, and the human body search for different ways to get them out of the body, such as immune responses minimizing their efficiency [143]. To address this issue, scientists need to find a way for nanomaterials can overcome the forces driving them out of the body and achieve an increased safety-to-risk ratio.

The toxicity of metallic nanomaterials is not limited to human health. The excessive use of nanomaterials is also likely to have adverse environmental effects [144]. As metals are not easily degraded, improper disposal of metallic nanomaterials causes pollution [145]. Nanoparticles can easily enter the bodies of humans and other organisms through the skin due to their ultra-fine sizes [146]. They can also get suspended in the atmosphere and travel long distances [147]. Nanoparticles not only cause air pollution but can also have harmful effects on soil and groundwater [148]. This issue can be addressed by developing biodegradable nanomaterials such as polylactic acid (PLA) and polyglycolic acid (PGA) [149]. For this purpose, they need to evaluate the complete life cycles, such as fabrication, storage, distribution, application, and disposal of nanomaterials [150]. In this way, nanoparticle contamination and pollution can be controlled.

Another challenge to nanobiotechnology is the limited understanding of nanomaterials, their characteristics, and their potential toxic effects. The efficiency of nanomaterials is limited by their complex nano-systems [151]. Very little literature and published research are available about nanomaterials and their potential risks [152]. There is not a single FDA-approved nano-antibiotic available yet for human utilization despite their remarkable antimicrobial activity [153]. Nanobiotechnology experts, researchers, and developers need to work together to understand this revolutionizing technology better. Also, the knowledge associated with nanomaterials should not be preserved. It should be shared between experts, research bodies, and even nations worldwide because that is how the research community can work together as a team. Employing machine learning and artificial intelligence for modeling the ideal nanostructure designs and understanding the interaction between nanomaterials and living cells is also a challenge to nanobiotechnology [154]. If overcome these challenges efficacy and efficiency of nanomaterials will ultimately be increased. Nanomaterials could be better optimized as therapeutic agents for target drug delivery by overcoming these challenges,

and hence financially effective nanobiotechnology techniques will be developed. To launch the safe and proper commercialization of nanotechnology and its applications, authorities must make definite policies.

13. FUTURE IMPLICATIONS

As discussed in the sections above, different factors, such as over/misuse of antibiotics, their inappropriate prescriptions, and inappropriate utilization for livestock production, have led to the emergence of antibiotic-resistant pathogens. Various strains of bacteria, viruses, fungi, and parasites have developed resistance to most classes of the existing antibiotics and are therefore known as "superbugs" [155]. These superbugs can potentially cause various diseases that cannot be treated with the available classes and generations of antibiotics and can result in outbreaks and hence, pandemics [156]. However, nanotechnology has the potential to prevent such pandemics. Nanotechnology can overcome traditional antimicrobials' limitations and restore antibiotics' lost activity [157]. The threats of pandemics could be addressed by nanomaterials' antimicrobial potential and applications [158].

There are different nanotechnology-based tools available that can prevent pandemics by combating the antibiotic-resistance phenomenon of superbugs. This goal could be achieved by practicing the clinical applications of nanomaterials, such as diagnosis, prevention, drug delivery, vaccination, and treatment [159]. Nanoparticle-based biosensors have the ability to rapid detection of pathogens. For instance, the recently developed nano-biosensors for detecting SARS-CoV-2 [160]. FDA has approved 49 nano-based devices for the diagnosis of COVID-19 [161]. Many nanoscale biosensors have been created to diagnose infections such as HIV, influenza, etc. [162]. The nano-delivery systems can be used for accurate target drug delivery, a limitation of traditional drug carriers [163]. For example, liposomes, polymeric nanoparticles, nanocrystals, and dendrimers are potential drug carriers [164].

Similarly, the limited efficiency of traditional vaccines can be addressed by developing nanoparticle-based vaccines, which are much easier to design and synthesize [165]. Various vaccine nano-carriers have already been designed as vaccination tools [166]. All these nanomaterial-based tools and strategies offer an excellent chance of winning the fight against antibiotic resistance by tackling most superbugs and hence, preventing an outbreak from becoming a pandemic.

14. LIMITATIONS OF BIOGENIC NANOMATERIALS

Despite the vast variety of applications, the use of nanomaterials also has various limitations. As discussed in the previous sections, the potential toxicity of nanomaterials to both, health and environment cannot be ignored. More than 400 studies have been reported concerning the toxicity and eco-toxicity of nanomaterials [167]. As using nanomaterials as antimicrobials can result in serious health issues in immunocompromised patients [168], therefore, no FDA-approved nanomaterial-based drug is available for human use yet [153]. Nanomaterials are not only potentially toxic, but can also cause air, water, and soil pollution [169]. The limited understanding of the complex nano-systems of nanomaterials is also a subject of concern. Large-scale utilization and handling of nanomaterials is a very challenging task. The lack of logistic knowledge for developing green-nanomaterials is one of the primary limitations of biogenic nanomaterials [170]. However, the notable and successful applications of nanomaterials in nano-biomedicine outweigh their limitations.

15. CONCLUSION

The continuous development of multidrug-resistant pathogens, also now known as "superbugs," can lead to outbreaks and pandemics and is, therefore, a global threat. As the current antibiotics and strategies are struggling to cope with this issue, developing novel, cost-effective, eco-friendly, and more effective alternative strategies is necessary. Nanotechnology is one of these strategies. Nanomaterials-based tools such as nano-biomarkers, nano-biosensors, etc., can solve the problem of antibiotic-resistant and prevent pandemics as per their potential applications in different areas such as diagnostics, prevention, vaccination, and treatment. Although, this technology has certain challenges to overcome, for which researchers are coming up with effective solutions.

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17. CONFLICT OF INTEREST

The authors declared no conflict of interest.

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