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Overview on Bacterial Resistance and Nanoparticles to Overcome Bacterial Resistance

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ABSTRACT

Microbial infections have been the leading cause of death throughout history. This was changed when antibiotics were discovered, causing an increase in life expectancy from 48 years to 72 years. However, this golden era might end very soon. Bacteria have evolved resistance against antibiotics using different pathways. Therefore, restrictive policies about using antibiotics should be implemented by the healthcare system to prevent the further spread of bacterial resistance. However, these policies might not be enough without discovering or synthesizing new antibiotics. Antibiotics synthesis or discovery is a lengthy, tedious multistage process. Moreover, the development of bacterial resistance against any newly developed antibiotics takes around 10 years. Therefore, there is a need to find another strategy to retain the current available antibiotics activity against micro-organisms. Nanotechnology is a cutting-edge science that has been emerged few decades ago, it is concerned with producing fibers or particles in the nanometer scale. In literatures, nanoparticles were shown to improve the drug solubility, bioavailability, modify drug pharmacokinetics, increase drug stability, target drug into certain sites and moreover, were proven to overcome some developed resistance mechanisms against anticancer drug (e.g. Efflux mechanism). Recently, nanotechnology techniques have been applied to combat microbial infections and they were proven to be able to overcome the bacterial developing resistance mechanism. In this review, we are presenting a historical background of antibiotics and discussing some bacterial developed resistance mechanisms as well as stating different nano-based formulations that were developed and proved to be effectively potentiate the antibiotic activity against some resistant micro-organisms.

Keywords: *Antibiotics; Resistant bacteria; Mechanisms of bacterial resistance; Nanoparticles*

INTRODUCTION

Infectious diseases are one of the leading causes of morbidity and mortality worldwide [1,2]. Bacterial infections are treated primarily by antibiotics, but over the last few decades, bacteria have developed microbial resistance to most antibiotics (ABs) available in the market[3]. This will led eventually to the emergence of pan drug-resistant (PDR) organisms[4]. PDR bacterial pathogens ,also known as superbugs, are resistant to all

known Abs and were identified in more than one country since 2008[5,6]. World health organization (WHO) and the center for disease and control prevention (CDC) pay much attention to the increased resistance developed by bacteria towards antibiotics [6,7]. Lack of effective ABs might render minor surgeries life- threatening intervention and be the leading death[1,8] worldwide as seen with the current pandemic COVID-19 infection [9,10].

Many resistant mechanisms developed by bacteria were identified such as (1) enzyme inactivation, (2) reduction of cell permeability, (3) alteration of the target active site and (4) increased ABs efflux due to efflux pumps over-expression. Additionally, some phenotypic features might be charctersing some bacterial strains such as biofilm formation and quorum sensing, this render them more resistant to the action of ABs[7,11].

Considering the above, it is clear that the current ABs are not enough to control microbial infections, however, developing a new nucelus of antibiotic cannot be considered as a solution for the current disaster, not only because it is a time consuming and expensive process but also, the time frame for bacteria developing resistant to any newely developed ABs is around 10 years [3,12,13]. Therefore, there is a high demand to find alternative strategies to combat infectious diseases caused by bacteria. Nanotechnology is a cutting-edge science that is interested in production of fibres [14–16] and particles [17–22]in the nanometer scale Nanoparticles (NPs) are particles have a size range from 10 to 1000 nm [19,23] and they are considered as a promising and effective strategy to combat microbial infections and their developed resistance [20,24]. This review explores the recent literature in this area, discusses the main causes and mechanisms of bacterial resistance and how NPs can provide a solution for these problems while using conventional ABs.

The fight against infections throughout history

Until the last century, infections have been the leading cause of death throughout history. Pharos and Greece realized the benefit of using fungi to cure infections (2650-2600 BC) [25]. After that, physicians used unexplainable savage methods to cure infections like bloodletting [26]**.** In modern history, until the nineteenth century, infections were cured with a bizarre collection of chemicals, including ammonia, lithium or even Sulphur. Until the beginning of the twenty century, Paul Ehrlich innovated the concept of chemotherapy and creating anti-infective drugs. He developed the first synthetic arsenic-based drugs, Salvarsan, in 1910 [27]. Salvarsan was the first AB ever used to treat syphilis more than 100 years ago. He concluded the use of Salvarsan as an anti-infective from dyes that stained only bacterial cells. Later, Sir Fleming noted the growth of mould in a contaminated Petri-dish. Surprisingly, something suspended the growth of bacteria in that Petri-dish. Later he discovered Penicillin (Pen) after studying this incidence[28]. The pen is naturally produced from fungi in a process known as antibiosis. Antibiosis is the ability of microorganisms to produce chemicals to kill other microorganisms[29]. The production of Pen by antibiosis had some limitations such as further purification steps are required to be given to patients [30]. Upon discovery of the chemical structure of Pen by Dorothy Hodgkin[31], Pen was manufactured chemically on a large scale[1,27,32] and was able to control many infectious diseases. Pen was considered a magic bullet that cured many previously incurable diseases[33]. The Pen was a simple and safer solution to cure infectious diseases that were previously fatal.

During 1940-1960 (the golden era of ABs), scientists discovered many other ABs produced by micro-organism through antibiosis [29] as presented in **Table 1** and **Figure 2**. Astonishingly, 64% of the discovered ABs are only found in Filamentous actinomycetes [3,13]. These classes of ABs are still in clinical use after more than 50 years.

Later on, many synthetic or semi-synthetic ABs were discovered and introduced to the clinical field[42]. Synthetic or semi-synthetic ABs are chemically derived from natural ABs. Synthetic or semi-synthetic ABs have a higher potency with lower doses and side effects. Quinolones are the fourth most used class of ABs after Penicillins, Macrolides and Cephalosporins in the US outpatients, and they are synthetic[43].

The most used semi-synthetic AB in outpatients is Azithromycin (AZI)[43]. AZI is a large molecule of 15 membered ring invented by Slobodan Dokic in 1980 and patented in 1981. AZI structure is shown in **Figure 1**. Pliva and Pfizer owned the license for mass production worldwide[44,45].

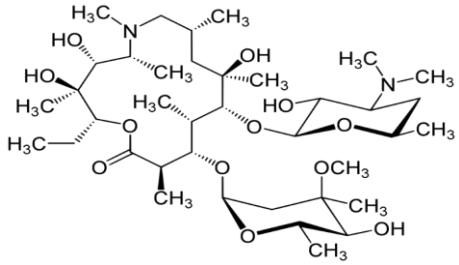

Figure 1. Structure of AZI

AZI was semi-synthesized from erythromycin (ER) to overcome ER disadvantages[45]. ER has a very short half-life of 1.5 to 2 hours. On the other hand, AZI has a longer half-life up to days in lung tissues. AZI attach to the 50S subunit in the bacterial ribosome. That leads to the inhibition of translation of mRNA and protein synthesis. The higher activity of AZI is due to the superior pharmacodynamics properties of AZI over ER.

Table 1. Examples of different ABs with their natural source

Bacterial		Fungal	
Antibiotic	Source	Antibiotic	Source
Mupirocin	*Pseudomonas fluorescens*[34]	Penicillins	*Penicillium chrysogenum*[28]
Polypeptides	*Bacillus Brevis*[35]	Cephalosporins	*Acremonium chrysogenum*[36]
Macrolides	*Saccharopolyspora erythraea*[37]	Fusidic acid	*Fusidium coccineum*[38]
Tetracyclines	*Streptomyces aureofaciens*[39]		
Polymyxins	*Paenibacillus polymyxa*[40]		
Chloramphenicol	*Streptomyces venezuelae*[41]		

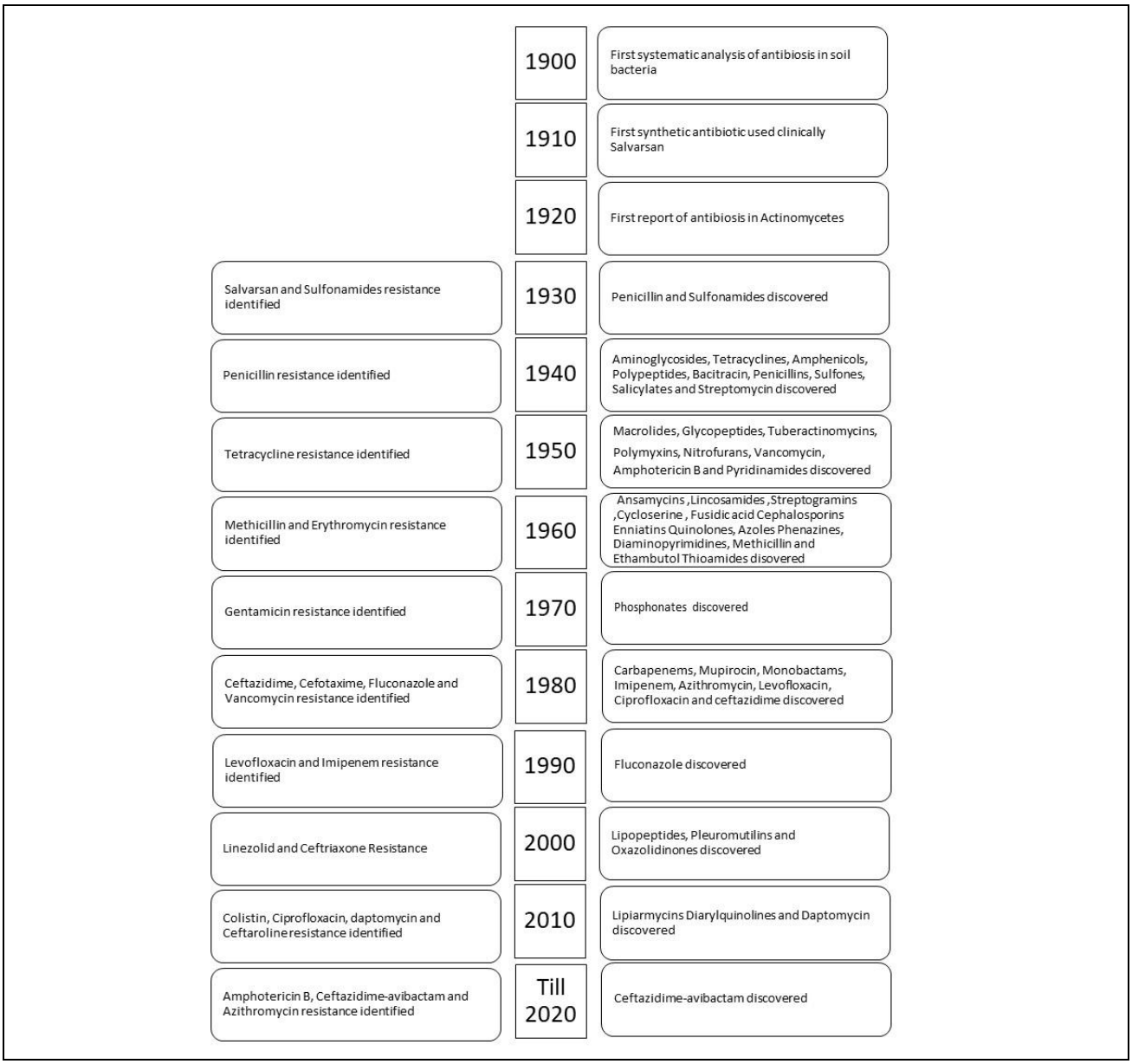

Figure 2. The timeline of discovering ABs and development of bacterial resistance [3,13]

AZI has a large volume of distribution. Although serum concentration (conc) remains low, it concentrates readily within tissues. AZI is distributed 200 times higher in lung tissue than the serum. AZI higher activity is related to its intracellular activity. AZI has a broad-spectrum activity against Gram-positive and Gram-negative bacteria, including *Bordetella pertussis* and *Legionella* species. Also, AZI is active against *Mycoplasma pneumoniae* and *Treponema pallidum*. Also, studies concluded that AZI has antiviral activity in cystic fibrosis [46]. These advantages lead to the high use of AZI in the medical field.

However, creating new synthetic ABs is a complicated process that consumes a tremendous amount of money and time. Unfortunately, the potency of the new AB would diminish within ten years due to bacterial resistance (BR), as shown in **Figure 2** [3,13]. Without a practical solution of BR, the results will be globally catastrophic. So, first, we need to understand the flaw in conventional ABs, so we can develop strategies to overcome BR.

Mechanisms of ABs

ABs kill bacteria through the inhibition of essential cellular processes. AB can attack a single target in the bacteria as presented in **Figure 3** and **Table 2** such as: cell membrane, cell wall, protein synthesis or bacterial enzymes [11,47–49]. Single process suppression increases the possibility of bacteria developing resistance against ABs [50]. Also, ABs are only bactericidal when used in a conc higher than the minimum inhibitory concentration (MIC).

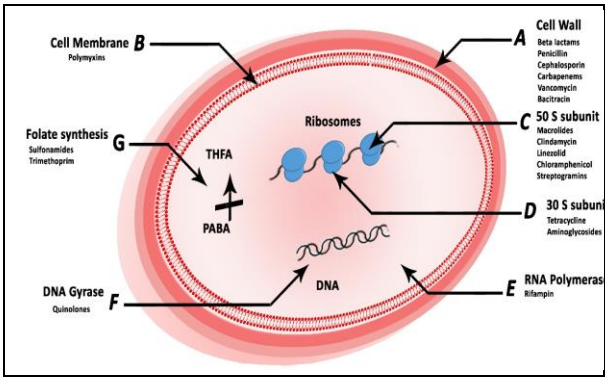

Figure 3. Mechanisms of antibiotics against bacteria; antibiotics can attack different sites in the bacteria resulting in their death such as: Cell wall (A) Cell membrane (B), 50S subunit (C), 30S subunit (D), RNA polymerase (E), DNA Gyrase (F) and Folate synthesis (G).

The development of bacterial resistance

Bacteria accomplish resistance in three steps at least: 1) gaining of resistance genes by microbes, 2) resistance genes expression, 3) selection for microbes with resistance genes[59].

First, bacteria gain resistance to single or multiple drugs through horizontal gene transfer through either transformation, conjugation, or transduction[60]. Also, bacteria can acquire resistance genes by spontaneous mutation of existing genes [61]. Multiple drug resistance occurs when a bacterial cell with one type of drug resistance gene develops another kind of drug resistance gene. Second, microbes express the resistance gene in response to AB drug. Third, resistance becomes widespread when selecting microbes that express resistance genes against the antimicrobial drug. This selection process favors resistant bacterium. Finally, developing resistance occurs whenever microbes are exposed to the AB, yet not eradicated (either by the AB itself or by the microbicidal effects of the AB itself or by microbiostatic effects of the AB followed by killing by the host's immune system gene [60,62].

Causes of bacterial resistance

1. *Poor patient compliance* plays a significant role in conducting this process where there is a high chance of developing resistant bacteria, upon application of ABs either for a shorter or longer time than it should be administrated[62]. Poor patient compliance leads to BR in the case of microbiostatic drugs, which inhibit but do not kill microbes completely, more than microbicidal drugs. As it allows some microbial cells to live and form resistance when exposed to the AB [63]. When a patient on an AB misses scheduled doses or takes an insufficient number of doses, this will increase the chance of acquiring AB resistance because the offending microbes are exposed to the AB but not wholly killed [64]. Poor patient compliance with short elimination half-lives drugs is a problem because these drugs have small dosing intervals, and the number of required doses for achieving MIC is high [64]. Even when patients are given the correct number of doses at the right times, there are still chances favoring AB resistance due to events within each dosing interval [64].

2. *Misuse of ABs*

Since the discovery of Penicillin in 1928, ABs are extensively used in various diseases. Even if it is not clinically needed. On the other hand, the overuse of ABs is the main reason for resistance evolution. Many epidemiological studies linked the ABs high consumption to the existence of resistant bacterial strains.

3. *Inconvenient prescribing and drugs regulations*

The unnecessary prescribing of antibiotics is also the main drive of bacterial resistance. Studies claim that in 30% to 50% of cases in the US, the AB of choice or the duration of therapy is inappropriate[3]. Also, many

Table 2. Classes of ABs, their target and the primary mechanism of resistance

Target	Class	Example	Mechanism of resistance	Reference
Cell wall	Beta lactams	Amoxicillin	Enzymes, target modification and permeability barrier	51
cell wall	Carbapenems	Meropenem	Enzymes, efflux and permeability barrier	52
cell wall	Glycopeptides	Vancomycin	target modification	53
cell membrane	Lipopeptides	Daptomycin	target modification	54
DNA enzymes	Quinolones	Ciprofloxacin	efflux and target modification	55
RNA enzymes	Rapamycin	Rifabutin	enzymes, efflux and target modification	51
30S subunit	Aminoglycosides	Amikacin	enzymes, efflux and target modification	51
30S subunit	Tetracycline	Doxycycline	enzymes, efflux and target modification	51
50S subunit	Oxazolidinones	Linezolid	efflux and target modification	51
50S subunit	Macrolides	Azithromycin	enzymes, efflux and target modification	56
50S subunit	Chloramphenicol	Chloramphenicol	enzymes, efflux and target modification	57
Folate synthesis	Sulfonamides	Sulfadiazine	enzymes, efflux and target modification	58
Folate synthesis	Trimethoprim	Trimethoprim	permeability barrier and target modification	51

third world countries have no strict laws to control the use of AB. This situation has a fundamental role in increasing resistance. Strictly controlled guidelines of prescribing have to be applied worldwide. The local authorities would monitor these guidelines [65].

4. The high use of ABs in the agriculture and cattle industry

In the whole world, ABs are highly used as growth supplements in the cattle and plant industry. 80% of the ABs produced in the US is estimated to be used in the cattle industry[3]. ABs have a beneficial role in the overall health of cattle, with a higher yield. However, the overuse of ABs increases the chance of bacterial resistance. Also, resistant bacteria in cattle can be transferred to humans through food. In addition, a small dose of ABs is consumed in food, which will increase the chance of bacterial resistance.

Moreover, up to 90% of the used ABs will reach the soil through animals' urine and stool. Besides, the use of ABs in agriculture affects the nature of bacteria in the soil. ABs' strict regulations in health care systems have to be conducted and monitored through governments[66].

5. Recently, many pharma companies suspended their pursuit to discover or invent in developing new ABs. Due to the low profit margin of ABs. Depending on two facts, first, ABs are described as an acute disease for only a short period. Second, microbial resistance will arise inevitably for the new AB. Eventually, the need for the new AB will decrease soon. In financial meaning, the expected profit from AB sales does not equal the anticipated economic profit from drugs treating chronic diseases like hypertension. Patients take an antihypertensive agent for an extended period, and no resistance mechanism might arise soon for the antihypertensive mechanism of action[67]. Hopefully, the threat of bacterial resistance and the new governmental regulations would revive the research for new ABs[42,68].

Bacterial resistance pathways

Bacteria resist AB through either cellular mechanisms or phenotypic feature as shown in **Figure 4**

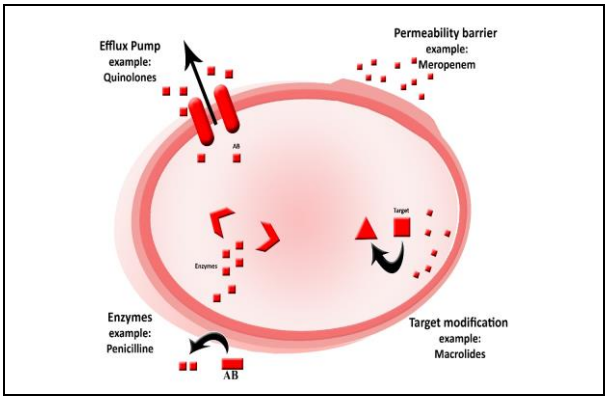

Figure 4. The cellular mechanisms of bacterial resistance

Cellular mechanisms of BR

Decrease intracellular concentration of ABs

Decreased uptake and/or increased efflux of AB from the microbial cell [69] are two essential resistance mechanisms. Reduced uptake of AB and/or use of transmembrane efflux pumps that prevent the conc of ABs from increasing to toxic levels within the microbial cell. Many bacteria are MDR through decreased uptake

and/or increased efflux of ABs. For example, the low sensitivity of *Pseudomonas aeruginosa* to antibiotics is due to efflux [62]. Gram-negative bacteria like *Pseudomonas aeruginosa* and *Escherichia coli* have an outer membrane surrounding a periplasmic space surrounding a peptidoglycan cell wall. The multidrug efflux pump of *Pseudomonas aeruginosa* consists of an inner membrane antiporter bound to the periplasmic area, which is linked to an outer membrane channel protein [70]. *Pseudomonas aeruginosa* becomes multidrug-resistant due to a mutation in the regulatory protein that usually represses efflux proteins-coding genes, leading to overexpression in efflux proteins[70].

Gram-negative bacteria have an outer membrane surrounding a periplasmic space (which contains a peptidoglycan cell wall) that covers an inner membrane. In contrast, Gram-positive bacteria have a peptidoglycan cell wall surrounding only a single plasma membrane. Gram-negative bacteria are less susceptible to Penicillin due to the extra outer barrier. That extra layer acts as a barrier for Penicillin to reach its site of action [60,62,70]. Bacteria can express resistance genes that cause overexpression of efflux to specific types of ABs, including Tetracyclines, Sulfonamides, Quinolones, Aminoglycosides, Chloramphenicol, Macrolides, and Streptogramins [51,62,70].

Target site modification

Resistance against Macrolides, Aminoglycosides, Tetracyclines, Linezolid, and Rifampin can be due to resistance genes coding for altered AB binding sites. For example, the binding site of macrolides is located on the 50s ribosomal subunit [71]. Each member of the family of Erm (Erythromycin resistance methylase) resistance genes codes for an N-methyltransferase which methylates an adenine of 50S ribosomal subunit that is near the binding site of Macrolides. The methylation blocks binding by Macrolides, so resistance against Macrolides is obtained. Erm resistance genes are located on plasmids or transposons [70]. Another approach of target site modification, bacteria resist Sulfonamides through up-regulation of the target enzyme (Di-dihydropteroate synthase).

Enzymes

Covalent modification of the AB molecule inactivates its antimicrobial activity. Microbes can express drug resistance genes that code for degenerative enzymes. Covalent modification of the drug is considered a resistance mechanism against Beta-lactams, Aminoglycosides, Chloramphenicol, Tetracyclines, Macrolides, Quinolones, etc. For example, beta-lactamases hydrolyze the beta-ring of Beta-lactams, thereby inactivating the antibiotic activity of the beta-lactam molecule and becoming beta-lactam resistant. In addition, bacteria can express resistance genes that cause overexpression of efflux to specific types of ABs, including Tetracyclines, Sulfonamides, Quinolones, Aminoglycosides, Chloramphenicol, Macrolides, and Streptogramins[51,62,70].

Phenotypic feature causing resistance

Biofilms are formed by bacteria exposed to very high conc of ABs, thus causing chronic infections despite antibiotic treatment. Biofilms can be elaborated as five steps: 1) First, proteins from the human host (blood or tissues proteins) attach to a solid or liquid surface, forming a conditioning film layer. 2) planktonic bacterial cells attract and attach to the conditioning film through electrostatic, hydrophobic, or London dispersion forces. Third, bacterial cells divide and attract other planktonic bacterial cells, thus increasing the population of bacterial cells. 3) Irreversible attachment is formed once the number of bacterial cells rises above a certain threshold. Through quorum sensing, these bacterial cells enhance the expression of genes that causes synthesis and secretion of a matrix consisting of extra-cellular polymeric substance (EPS). The EPS matrix is the reason for biofilm resistance, having the following features. First, the EPS matrix accumulates and surrounds the population of bacterial cells. Besides, this EPS matrix consists of polysaccharides, proteins, and DNA. Second, the EPS matrix collects minerals, blood proteins, and debris from the surrounding environment. Third, the EPS matrix is well hydrated, and it's up to 95% H_2O[60,62,72–75].

The EPS matrix acts as a barrier to intact AB molecules' diffusion. This EPS matrix protects the bacterial population from the high conc of different ABs, often leading to chronic infections despite antibiotic treatment. Therefore, bacteria in biofilms are 1000 times more resistant to ABs than planktonic bacteria. AB molecules are much less likely to reach bacteria located deep within the EPS matrix and more likely to reach superficially located bacterial cells [76,77]. EPS matrix promotes the formation of new AB resistance mechanisms. The EPS matrix decreases the conc of AB in bacterial cells, exposing them to sub MIC without decreasing that conc abruptly to 0 [60,62,72–75,78].

Novel strategies

Governments or companies can finance research projects for developing new ABs. Also, governments have to conduct and control new protocols, guidelines and regulations to stop the emerging of new BR[79]. However, Bacteria could eventually develop BR for the new discovered AB. ABs that work on multiple sites of the bacteria can be a promising solution too. But searching for new, more effective ABs is very costly and time-consuming. Therefore, we need to develop new strategies to combat infections. These strategies have to revive the conventional ABs and decrease the emerging

of BR. Nanoparticles (NPs) could be a safer, cheaper and more accessible solution for now. As NPs have exceptional chemical and physical features that can help to overcome BR.

Nanoparticles

Paul Ehrlich is considered to be the first to implement the concept of targeted delivery systems. He named these targeted delivery systems " magic bullets", that could greatly improve drug therapy since 1954 [80]. However, the first research using NPs was for vaccination purposes by Peter Speiser in 1970 [80]. Since then, NPs have been extensively used for many research purposes. NPs can have versatile chemical and physical features depending on many factors. The building blocks of the NPs materials and the synthesis conditions are the main affecting factors. NPs have proven a higher activity as anticancer therapy. Besides, the FDA has already approved many anticancer, antifungal and antiviral NPs medications[81]. In literature, nanotechnology is applied to treat many types of diseases and overcome many side effects associated with the application of medication [81]. Moreover, nanoparticles were reported to combat infectious diseases in many ways such as (1) encapsulation or conjugation of ABs such as polymyxin B in Liposomal NPs to avoid the efflux mechanism. When liposome fuses with the bacterial cell membrane, it releases a high amount of AB into the bacteria without being detected by the efflux pumps[73,82,83]. (2) some other NPs such as metal-based NPs were reported to produce reactive oxygen species that can attack multiple sites in the micro-organism and thus reducing the possibility of bacteria developing resistance [20]. Deliver ABs to intracellular pathogens (liposomes) and increase the conc of AB at the site of action[24,73,84–86]. (3) packaging multiple antimicrobial drugs in the same NPs, is a robust approach to competing for resistance [83,87]. These approaches will be discussed in this review as follows:

1. Nanoparticles with multiple simultaneous mechanisms of action against microbes

Metal-based NPs are highly active as antibacterial NPs due to the multiple simultaneous mechanisms of action that they have. Metal-based NPs can damage cell membranes, photo kill bacteria, generate reactive oxygen species, disturb the ion homeostasis and damage protein, genes or enzyme[12,50]

There are different types of metal-based NPs, each of which uses multiple mechanisms to kill and/or inhibit the growth of microbes, making the development of drug resistance unlikely[78]. Bismuth-containing nano-particles (Bi NPs) combined with X-ray treatment can treat resistant bacteria [88]. In a recent study by Brown et al., Au NP with ampicillin bound to its surface (Au NP-AMP) killed MDR bacteria, including MRSA, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, and *Escherichia coli* K-12. Au NP-AMP probably had multiple mechanisms of antibacterial action, implying a low likelihood of the development of Au NP-AMP resistance. All bacteria tested express beta-lactamase and are resistant to ampicillin alone. Brown and colleagues rationalized that bacteria cannot carry out endocytosis and cannot take up Au NP by itself [89]. However, ampicillin can cross the cell envelopes of Gram-positive and Gram-negative bacteria and therefore have antimicrobial activity against both. Thus, ampicillin on the surface of Au NP allows Au NP-AMP to reach the bacterial cell wall. Brown et al suspect that at least two mechanisms of antibacterial action are at work. First, the presence of multiple ampicillin molecules on the surface of Au NP allows the Au NP-AMP to overwhelm the high conc of beta-lactamase expressed by these bacteria. Second, Au NP-AMP inhibits the transmembrane pump that catalyzes drug efflux from the bacterial cell [89].

2. Multiple antimicrobial agents packaged within the same NP

Multiple antimicrobial compounds can be packaged in the same NP. It is doubtful that bacteria can develop resistance to the various agents within these NPs[90]. It would require multiple simultaneous gene mutations in the same bacterial cell. Also, using various drugs within the same nanoparticle can result in a higher potency, higher antimicrobial efficacy, and overcome existing mechanisms of drug resistance in microbes relative to single drug use [73,83,87]. Most examples include two agents packaged within the same nanoparticle. For instance, vancomycin encapsulated in chitosan NP is effective against vancomycin-resistant *S. aureus* (VRSA) [73]. Au NP capped with vancomycin (Au Van NPs) had activity against vancomycin-resistant *Enterococcus* (VRE) and against *Escherichia coli* that was 64 times higher than vancomycin alone [73]. In another study, Au NPs coated with ciprofloxacin had increased potency against VRE [73].

3. Nanoparticles that overcome decreased uptake and increased efflux of the drug by bacteria

Liposomes and dendrimers can overcome the resistance mechanisms of decreased uptake and increased efflux of drug from the bacterial cell. A liposome is composed of one or more lipid bilayers forming a sphere-shaped vesicle. Each of these bi-layers contains amphipathic lipid, often phosphatidylcholine, and commonly includes cholesterol to increase the rigidity of the membrane[82,83]. The lipid bilayer of a liposome fuses quickly with the microbial cell's plasma membrane, causing a rapid release of its content of antimicrobial agent into the microbial plasma membrane or cytoplasm [83,82,73]. AZI was reported before to have a higher potency when encapsulated in liposomes, as shown in **Table 3** [91].

Table 3. Previous studies on AB-NPs using safe carriers, and the efficacy against tested pathogens

Antibiotic used	Carrier	Organism tested against	Result	Reference
Doxycycline	methacrylate / Polymeric	*Enterococcus faecalis*	Inhibit biofilm	[98]
Enrofloxacin	hyaluronic acid/chitosan / Polymeric	*Staphylococcus aureus*	Increased potency	[99]
Vancomycin	PLGA / Polymeric	vancomycin-intermediate and methicillin-resistant *Staphylococcus aureus*	Higher potency against MRSA	[92]
Rifampicin	alginate/chitosan / Polymeric	methicillin-sensitive and resistant *Staphylococcus aureus*	Higher potency	[100]
Ofloxacin	polycaprolactone / Polymeric	*Escherichia coli*	Increased activity	[101]
Vancomycin	chitosan / Polymeric	*Staphylococcus aureus*	Higher potency	[102]
Sparfloxacin and Tacrolimus	PLGA / Polymeric	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	Anti-infective and anti-inflammatory both in-vitro and in vivo	[103]
Rifapentine	PLGA / Polymeric	*Mycobacterium tuberculosis*	Higher potency	[104]
Doxycycline or Vancomycin	cationic or zwitterionic lipids and PLGA / SL NPs	methicillin-resistant *Staphylococcus aureus* and *Mycobacterium smegmatis*	Higher entrapment longer duration	[94]
Clarithromycin	chitosan / Polymeric	*Streptococcus aureus* and *Pseudomonas aeruginosa*	Higher potency	[105]
Ciprofloxacin and Azithromycin	PLGA / Polymeric	*Pseudomonas aeruginosa*	Reduced biofilm formation	[106]
Azithromycin	Liposomes / Phospholipids	*Bacillus subtilis* and *Pseudomonas aeruginosa*	Higher potency	[91]

Table 4. Comparison between the different types of NPs carriers and the relevant toxicity or inflammatory response to each one of them

Type of NPs	Side effect		Reference
	Toxicity	inflammation	
Liposomal	No	No	[107]
Polycaprolactone	No	No	[108]
Polyacrylate	No	No	[74]
Silica	moderate	moderate	[109]
PLGA	Low	No	[110]
Chitosan	Yes	Yes	[111] [112]
Silver	Yes	Yes	[113] [114]
Gold	No	Yes	[115]
ZnO	Yes	Yes	[116] [117]
Iron oxide	Yes	Yes	[118]
TiO_2	Yes	Yes	[119]
Copper	Yes	Yes	[120] [121]

4. NPs that combat intracellular bacteria

NPs have also been used to combat intracellular bacteria by phagocytosis. NPs, including poly lactic-co-glycolic acid (PLGA) NPs, are small enough to be phagocytosed by host phagocytes that contain intracellular microbes. Once PLGA NPs enter the host cell, NPs release AB, which combats these intracellular microbes [87,82,73]. Vancomycin-PLGA NPs were more potent against methicillin-resistant *Staphylococcus aureus*[92], as shown in **Table 3**. NPs can release a high conc of ABs inside infected host cells while maintaining the total dose of AB administered low[82]. NPs can combat

intracellular microbes in alveolar macrophages. Microbes can protect themselves from ABs by living intracellularly[73]. Attachment of mannose to nanoparticles containing antimicrobial drugs allows them to be efficiently targeted to alveolar macrophages, which heavily express mannose surface receptors[73]. Liposomes containing ciprofloxacin and conjugated with mannose were administered by the pulmonary route and had high selectivity for alveolar macrophages [73].

5. NPs that deliver ABs to the site of infection

Finally, NPs target antimicrobial agents to the site of infection, so achieving a higher conc of AB at the infected site, thereby overcoming existing resistance mechanisms with a minimal dose and adverse side-effects [93]. Ampicillin, conjugated with gold NPs, was active against MDR Isolates of *Pseudomonas aeruginosa*, *Enterobacter aerogenes* and Methicillin-Resistant *Staphylococcus aureus*[89]. For nanoparticles targeting intracellular bacteria, NPs targeting the site of infection can release a high conc of antimicrobial drugs at the site of action while maintaining the total dose of medicine administered low. Doxycycline had a higher potency against intracellular pathogens when it was encapsulated in lipid polymer hybrid NPs[94], as shown in **Table 3**. Again, the high local conc at the site of infection also kills the infecting bacteria before developing resistance. At the same time, the lower total dose minimizes the probability that bacteria outside the site of action of the nanoparticles produce drug resistance. NPs can be targeted to sites of infection either passively or actively. Passively-targeted NPs selectively undergo extravasation at sites of infection, where inflammation has led to increased blood vessel permeability. Actively targeted NPs have ligands (e.g. antibodies) that bind to receptors (e.g. antigens) at sites of infection. The antimicrobial action of nanoparticles can be activated by certain stimuli, such as low pH or reactive oxygen species (ROS). Drug release can be regulated and targeted at the site of action by magnetic guidance or radiofrequency [87].

Limitation of NPs usage in the medical field

Metallic, polymeric, liposomes and solid lipid (SL) NPs can be used in drug delivery systems. Metal-based NPs were active against resistant bacteria in many previous studies [12,50]. However, most metallic NPs can cause inflammation or cytotoxicity, as shown in **Table 4** [95]. On the other hand, polymeric, SL and liposomal NPs are relatively safe. Furthermore, there are no known side effects for polymeric, SL and liposomal NPs. Besides, FDA has previously approved nanomedicines from the relatively safe NPs carriers[47,96,97].

Many studies were conducted on ABs-NPs using polymeric, SL and liposomes as carriers, as shown in **Table 3**, where AB-NPs had a higher potency against bacteria than the plain AB alone. However, no studies have tested the activity of AB-NPs against MDR, XDR and PDR microorganisms. As many AB-NPs can represent a robust method to overcome resistance as they are both practical and safe.

CONCLUSION

BR is considered a global concern by the WHO and CDC. There are many reasons for BR that needs to be rectified by governmental actions. However, these actions would only delay the post ABs era. Inventing new ABs is another solution. But it is a very costly process. In addition, bacteria will evolve resistance for that new AB. More practical strategies have to be considered for a cheaper and more accessible solution. NPs are a promising solution, that has proven to be active against many MDR pathogens. Unfortunately, some NPs have safety issues that hindered the FDA from approving metal-based NPs. However, polymeric, SL and liposomal NPs are safe and have not been tested against MDR pathogens. We recommend testing the activity of relatively safe NPs against MDR pathogens.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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