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Review Article

APPLICATION OF NANOANTIBIOTICS APPROACH AGAINST ANTI-BACTERIAL RESISTANCE

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ABSTRACT

Despite the fact that we live in an era with unique and advanced technology for revealing underlying molecularly creating new drugs and disease mechanisms, infectious illnesses remain one of the world's major health issues. Antimicrobial agents now available against pathogenic microorganisms are insufficient to combat the problems posed by novel multidrug-resistant (MDR) infections. Antimicrobial drug restrictions are producing negative side effects and the development of multiple drug resistance. Drug resistance will necessitate the use of high-dose antibiotics, resulting in severe toxicity and the development of new medicines. Nanoantibiotics, a new type of antimicrobial agent that combines antimicrobial compounds with nanoparticles, has been created to solve these shortcomings. Additionally, previous reports stated that the pharmacokinetics profiles and have quicker ingestion in circulatory framework. In this subject, we will clarify the various sorts of nanoantibiotics, their instrument of activity, key targets and medication discharge components. We will likewise portray some significant microbial elements that will influence the activity of nanoantibiotics.

Keywords: Infectious disease, Antimicrobial agents, Drug resistance, Nanoantibiotics

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INTRODUCTION

Background of antibiotics: global threats, market value and statistics

Antibiotics are antimicrobial agents which are used to treat diseases caused by bacteria. After Alexander Fleming founded penicillin in 1928, a variety of antibiotics was designed to cure diseases caused by bacterial pathogens. Over time, bacteria started to develop resistant towards antibiotics as lack of awareness, management issues and misuse of antibiotics. This has become a concern to all countries in the world [1]. To address this problem, the World Health Organization has chosen to improve and deploy a scientific technique for studying antimicrobial resistance (AMR). In a recent study, a survey for the consumption of antibiotics was conducted. It was found that an increase of 65% in global intake of antibiotic. The developed counties were observed to have a higher rate than underdeveloped countries [2].

Mechanisms of resistance

Some bacteria have special properties that can inhibit the effects of antibiotics, thus preventing the antibiotics to destroy them. There are different types of mechanisms that cause resistance of antibiotics. For example, It has been discovered as a mutation that affects the bacteria's 30S ribosome subunit [3]. This form of resistance is thought to be produced by an amino acid change in the protein S12, which is found in the small subunit [4]. Streptomycin-resistant bacteria have been demonstrated to have ribosomes that do not bind to streptomycin [5]. Antibiotic binding was observed to be inhibited when the 30S protein S12 was switched. Radioactive streptomycin does not bind to protein S12, according to studies. This demonstrates that this protein is one of the main antibiotic binding sites but not the entire binding site [6]. A change in protein S5 of the 30S subunit causes this sort of mutation [6]. The protein S5 was changed by a single amino acid substitution, according to analysis [4]. Drugs cannot attach to the mutant bacteria's ribosomes, indicating that the mutation has changed or destroyed the drug's binding site. The amount of resistance grows as the capacity of the ribosomes to bind the drug decreases, according to studies of a range of mutant bacteria with various phenotypes. When the 50S ribosomal subunit is changed, erythromycin resistance develops. In S. aureus, however, the mutation is present in the 23S rRNA gene. It was discovered that a peptide of the 50S ribosomal protein 50-8 changes when ribosomal proteins from resistant and susceptible E. coli strains are compared [5]. Many erythromycin-resistant mutants have 50S ribosome subunits that do not bind radioactive erythromycin. It has many pleiotropic effects in mutant E. coli, including resistance to certain macrolide antibiotics and decreased peptidyl transferase activity on ribosomes [3]. In fusidic acid-resistant bacteria, this resistance impairs the protein synthesis machinery. Fusidic acid is a steroid-type antibiotic that inhibits G factor protein activity [8]. Because the G factor of fusidic acid-resistant bacteria has been changed, the antibiotic can no longer adhere to it [9]. Resistance to fusidic acid is required for research on the translational factor EFG.

Limitation of conventional antibiotics

In recent years, the development of new antibiotics has decreased significantly. Antibiotics for Gram-negative bacteria have not been developed in the last 40 y. This demonstrates that antibiotic resistance has become a major issue, resulting in many fatalities and illnesses. In certain circumstances, such as conflict, disaster, or malnutrition, the importance of these infections is lethal. Antibiotic resistance, according to the World Health Organization (WHO), can cause diseases, and some of them can be deadly if antibiotic resistance is not addressed swiftly. In Europe, some 25000 persons die because of bacterial infections with multiple medication resistance.

Antibiotic resistance diseases frequently affect patients who are grouped together and treated with antibiotics with aggressive effects. Antibiotic resistance has been a source of concern in recent studies. People have spoken out against the rising number of people infected with lethal aggressive infections because of antibiotic resistance each year, as well as the large number of deaths that occur from this condition. Unfortunately, the pharmaceutical industry is responding to this scenario by deploying innovative antibiotics to treat resistant bacterial strains, even though antibiotics are still misused across the world. This has become a concern not just for healthcare sectors, but also for countries throughout the world's economies.

Self-medication and overdosage are among the main causes for antibiotic resistance. Other factors include low economic status of people, low health education and unavailability of doctors on time. As a result, patients are forced to ask from a nearby pharmacist or

self-medicate themselves that may cause an increase of antibiotic resistance [4]. Currently available antibiotics are just temporary solutions to cure infections.

Development of nanoantibiotics: an alternative ways paradigm

The nanotechnology-based interventions have entered to health and biological sciences because of the multidisciplinary nature of nanoscience. Nanomaterials are materials with a size around 1-100 nm. Nanomaterials consist of many shapes and sizes, which make them suitable for a lot of applications. When a material is reduced to a very small size, the properties of that material can exhibit dramatic changes. Healthcare sectors have received huge attention from nanotechnology among many fields. The nanoantibiotics are a recent invention which uses nanomaterials that possess antimicrobial potential or have the ability to enhance the efficacy of the antimicrobial drug [5]. When compared to traditional antibiotics, it provides several benefits such as absorption, durability, circulation, controlled release, and focused distribution. They are also affordable and versatile when it comes to antibiotic resistance [12]. Nanoantibiotics have been demonstrated to be more effective in treating infections caused by bacteria. Antimicrobial resistance will be addressed using these nano-based technologies as an alternative.

Objectives

The aim of this article was to look at how nanotechnology is being used in the treatment against resistance bacteria now and in the future.

Methods

This literature search was conducted using Web of Science, ScienceDirect PubMed, Google Scholar, and other online sources. The article search focused on nanotechnology, nanoantibiotics, mechanism of nanoantibiotics, advantages and disadvantages of nanoantibiotics. This article was searching original articles from 1972 till 2021.

Types of nanoantibiotics

Metal, metal oxides or composites

Most of the metal-based nanoantibiotics are possessing effective antimicrobial activities. For instance, metals like silver (Ag) and gold (Au) or metal oxides like zinc oxide (ZnO), copper oxide (CuO), iron oxide (FeO), etc., are possessed of antimicrobial potential [6]. Furthermore, these metals could differentiate prokaryotic and eukaryotic cells via metal transport systems and metalloproteins. The mechanism of metal-based nanoparticles to inhibit the bacteria. Due to the surface area to volume ratio, nanoscaled metal-based nanoparticles are very potent and this enable strong antimicrobial activities [7]. Recently, metal-based nanoparticles are used in antimicrobial applications and synthesis such as doping, nanocomposites and green synthesis. Metals are often doped with metal oxides in order to have better antimicrobial potential. For example, silver-doped zinc oxide (Ag-ZnO) had shown to improve antimicrobial activities against Staphylococcus aureus and Pseudomonas aeruginosa [8] while silver-doped titanium oxide (Ag-TiO) had shown to improve antimicrobial activities against Escherichia coli and Pseudomonas aeruginosa [9]. Silver nanoparticles have a high surface specific area, which will lead to excellent antimicrobial activity as compared with bulk metallic silver [10].

Recent progress has been made on the interface of phytonanotechnology where biosynthesis of metal and metal oxide-based nanoparticles are carried out by using plant-based pharmacologically active extracts [11]. Phytosynthesis has advantages like having entire green route in production, cost-effective, single-step and higher degrees of biocompatibility for nanoparticles synthesized. For example, iron nanoparticles synthesized from tea extracts were discovered to be non-poisonous to keratinocyte cells of human if compared to iron nanoparticles synthesized from sodium borohydride as a reducing agent [12].

Polymeric nanoparticles

Polymeric nanoparticles are composed of biocompatible and biodegradable polymers of natural or synthetic origin [13]. Polymeric nanoparticles based antibiotic systems help to enhance intracellular drug delivery and control therapeutic drugs released. They are being synthesized by conjugating or encapsulating the therapeutics in polymer backbone or core [11]. The polymeric nanoparticles systems are flexible in respect of functionalization and synthesis. At first, polymeric nanoparticles are started using non-biodegradable polymers like polyacrylates, polystyrene, polyacrylamide, etc., which will accumulate in the body and cause toxicity. Now, it is more concerned on the use of extractable and biodegradable polymers like poly-aminoacids, chitosan, poly-lactides, albumin, gelatin and alginates [13]. Polymeric nanoparticles-based antibiotics have better results in removing pathogens from the body, improving bioavailability, antibiotic protection from enzymatic and hydrolytic degradation as well as versatile routes of administration if compared to conventional antibiotics. In addition, they also have the advantages of size-shape and stability-controlled synthesis [11].

There are many polymeric systems for the treatment of microbial infections has been prepared. For example, (rifampin-azithromycin-PLGA (poly(lactic-co-glycolic acid)) are more effective if compared to antibiotics without PLGA in chlamydial infection [11]. Furthermore, ampicillin encapsulated in poly (isohexyl cyanoacrylate) (PIHCA) nanoparticles have improved the efficacy in treating *Salmonella typhimurium* infections in mice by 120-fold. Similarly, it is reported that ampicillin-encapsulating nanoparticles have controlled intracellular *Listeria monocytogenes* infection in mouse peritoneal macrophages efficiently [14]. It is also reported that various alginate polymer-based nanoparticles can improve anti-tuberculosis. Tobramycin-based polymeric nanoparticles have an impressive result against *Pseudomonas aeruginosa*. Various polymeric nanoparticles also successfully used against biofilms [11].

Fullerene and carbon-based

Fullerene (C_{60}) and other carbon-based materials such as graphene are being focus on recently due to their antimicrobial properties. The carbon nanotubes are made of pure carbon atoms with cylindrical nanostructures which are bonded covalently in hexagonal arrays. They can be graphene materials (GMs), multi-walled carbon nanotubes (MWCNTs) and single-walled carbon nanotubes (SWCNTs) [15]. The formation of SWCNTs and MWCNTs using graphene materials. These carbon nanotubes can prevent the bacteria's growth through various routes and thus can interfere with organisms. The exact mechanism and knowledge of the carbon based nanomaterials in exhibiting antibacterial potential still have to explore further [11]. Some researchers found out that photocatalytic production of ROS in eukaryotic cells and lipid peroxidation in prokaryotic cells are having antimicrobial mechanism of nanocarbon action. Graphene materials can also use as graphene quantum dots (GQD), graphene oxide (GO) and reduced graphene oxide (rGO) [11].

Currently, nanocomposite system of reduced graphene oxide iron oxide nanoparticles (rGO-IONP) has potentially controlled methicillin-resistant *Staphylococcus aureus* (MRSA) by chemical and physical multilation. Chemical damage is done by iron oxide nanoparticles (IONP) that increase the degradation of hydrogen peroxide (H_2O_2) by increasing its level when inflammation occur and formed OH radicals which are highly reactive via Fenton reactions. Efficient absorption of near-infrared (NIR) energy by reduced graphene oxide (rGO) that will be changed to heat causes physical damage to bacteria. The combined action of NIR and rGO-IONP has an effect on controlling bacteria in subcutaneous inflammations and speed up wound healing significantly during *in vivo* results [11]. The rGO and GO show toxicity towards *Escherichia coli* and *Staphylococcus aureus* [16]. Similarly, C_{60} show great antimicrobial activity against *Salmonella typhi* that have drug-resistant strain. There are multiple ways of colloidal use for graphene-based nanomaterials such as only graphene, colloidal nanohybrids and polymer stabilized graphene material. Nanohybrids of graphene are complex systems where usually metal nanoparticles like silver are attached on graphene material surface. The decorated fabrication has synergistic antimicrobial activities as proved in the case of silver reduced graphene oxide (Ag-rGO) nanocomposites, which are more effective than ampicillin against *Escherichia coli*. Moreover, Ag-rGO

nanocomposites have better inhibitory potential against *Escherichia coli* than *Staphylococcus aureus* [17].

Mechanisms of action of nanoantibiotics

In order to solve global problem of antibiotic resistance, nanoantibiotics is a new paradigm being developed to overcome this problem. This is because nanoantibiotics have various target or action sites that will prevent microbes from developing resistance genes against various killing mechanisms carried out by nanoantibiotics. Different nanoantibiotics have different mechanisms to fight against microbial infections. These include production of reactive nitric oxide (NO) and reactive oxygen species (ROS) that destroy cellular components, inhibition of DNA and enzyme synthesis, release of heavy metal ions with harmful effects, interruption of energy transduction by affecting electron transport chain reaction in transmembrane as well as adsorption to and break down cell wall or cell membrane [14].

Mechanism of action of metal-based nanoantibiotics has been evaluated in many studies. For example, silver and silver oxide nanoparticles have effective antimicrobial action against various drug resistant organisms. They exert antimicrobial action through multiple mechanisms and thus, they are very effective. Silver nanoparticles will release large amount of silver ions to change the cell membrane integrity and help in the interruption of energy transduction via electron transport chain. Besides, they also involve in damaging DNA of microbial cells [18]. Zinc oxide nanoparticles are another class of nanoantibiotics that act by accumulating inside the cells and release zinc ions. This will involve in production of hydrogen peroxide and cell membrane disruption. Titanium dioxide nanoparticles affect cell membrane integrity by generating ROS [14].

Furthermore, liposomal, carbon based, and different polymeric nanomaterials also being used as nanoantibiotics, all of them have own modes of action. Chitosan-based nanoantibiotics will increase permeability and cause rupture of cell membranes. They also involve in inactivation of enzyme of microbial. Carbon nanotubes will generate ROS that result in oxidative degradation of lipid, proteins and cell membranes. New class of nanoantibiotics containing fullerenes will involve in destruction of cell membrane integrity and increase activity of infiltrating neutrophils. These various mechanisms of action cause nanoparticles become good agents in targeting microbial machinery.

Drug release kinetics of nanoantibiotics

Drug release kinetics are important in determining the efficacy of a drug with nanoparticles. The efficacy of drug can be maximised by avoiding drug metabolism before it is transported to target site. Therefore, the drug needs to release from nanocarrier in a slower rate. However, controlled drug release is applied to maximise the effect to target site and to prevent adverse effects. These qualifications determine the effectiveness of nanoantibiotics [19].

Ultra-centrifugation, dynamic dialysis and continuous flow techniques are examples methods to determine drug release from nanoantibiotics. Since dynamic dialysis can avoid the dissociation of drug from nanoparticles throughout the study, so dynamic dialysis is usually used. On the other hand, another method will exert external pressure during dissociation [20]. To ensure controlled and targeted release of antibiotics, different nanocarriers with varying mechanisms and properties on drug release kinetics had applied. For instance, nano-emulsion, polymeric nanoparticles, liposomes and micellar systems [21].

The drug release kinetics of polymeric nanoparticles depend on diffusion, absorption and erosion of polymeric nanoparticles. Drug release by diffusion happens only when the erosion rate of polymer matrix is lower than diffusion rate from matrix. However, drug in nanoparticles will first burst release from the surface bound as contrast with drug within matrix. On the other hand, the drug release kinetics of liposomes depend on type and permeability of drug, constitution of lipid membrane as well as environmental factors. External stimuli like enzymatic degradation and protein interaction as well as pH and temperature that may alter drug release kinetics [22].

Nowadays, strategies to produce effective nanoantibiotics become centre of attention. To produce new nanoantibiotics, the drug is packed with polyelectrolytes that has improved antibacterial activity and drug dispersion [21]. By using covalent bond or anionic Gemini surfactant that can be degraded in acidic environment, the drug release of nanoantibiotics can be controlled. To have sustained release effect, cockle shell-based calcium carbonate aragonite-based nanomaterial is used [23]. Based on one of the studies, the drug will first burst release and then controlled release which is based on 2nd order release kinetics when using streptomycin-loaded chitosan-magnetic iron oxide nanoparticles (Strep-CS-MNP) compared to the physical mixture of these two substances. It also proved that Strep-CS-MNP has enhanced antibacterial activity against MRSA compare to the single agent of streptomycin [24].

Based on a current study, 90% of drug is released within 2.5 h when using single-walled carbon nanotubes (SWCNTs)-ciprofloxacin nanoantibiotic where carbon nanotube is one of the nanomaterials. It follows 1st order release kinetics and has 8 times more effective against *Escherichia coli* as well as 16 times more effective against *Pseudomonas aeruginosa* and *Staphylococcus aureus* compare to the single agent of ciprofloxacin [25]. According to another study, there is an enhanced penetration into biofilms and effectiveness against MRSA when using metal-carbenicillin framework coated mesoporous silica nanoparticles (MSN). This proves that combination of metal and antibiotics can improve antibacterial activity [26].

Microbial factors affecting the action of nanoantibiotics

Bacterial structural variations contributing to MDR

Resistance to antibiotics normally happens to gram-negative bacteria which has lipopolysaccharide (LPS) rich outer membrane [27]. This is because hydrophobic antibiotics cannot cross LPS membrane causes resistance to antibiotics but hydrophilic antibiotics can cross this membrane [28]. Furthermore, phosphatases, proteases and nucleases are enzymes that cause antibiotic degradation also give rise to resistance of gram-negative bacteria. Those bacteria that can produce penicillinase or cephalosporinase can degrade the antibiotics. However, the membrane negativity is provided by LPS of gram-negative bacteria so that the positively charged nanoantibiotics can attach and penetrate into the bacterial cell [29]. Besides, completely negative charge of nanoantibiotics is repelled by negatively charged membrane. Therefore, a nanoantibiotic carrier need to have hydrophobic and hydrophilic characteristics to achieve therapeutic therapy.

Variation in microbial growth rate

Theoretically, antibiotics including nanoantibiotics are active against dividing cells. However, there are some bacteria that resistant to several types of antibiotics especially insufficient rapid division in non-spore forming bacteria. These bacteria display some conformational changes at stationary phase that causes resistance to nanoantibiotics due to the insufficient nutrients and antibacterial activity [30]. Therefore, the stress response in slow dividing cells causes antimicrobial resistance. In short, the efficacy of nanoantibiotics largely dependent on microbial growth rate.

Biofilm formation in bacteria

Biofilm formation is a process where bacteria attached irreversibly and grow on a surface to form extracellular polymers as a biofilm. These polymers help in attachment and cell-cell communication [31]. Biofilms composed of polysaccharides, proteins, and DNA. However, these biofilm causes antibacterial resistance by forming poly-layered defence where it is impermeable to antibiotics. Biofilms also contains hydrolysing enzymes that causes antibiotic resistance. Besides, biofilm forming bacteria remain unaffected when facing stress responses which causes it to be more resistant to antibiotics. Its growth rate is also slow which causes it to resist antibiotic action. Therefore, biofilms help in gene transfer among different species, thus developing acquired resistant to other species also [32].

To inhibit biofilm-mediated MDR, polymeric or liposome drug delivery systems are applied [33]. However, polymeric based nanoantibiotics are recommended since it has extra beneficial

properties such as surface fictionalization, hydrophobic and hydrophilic materials encapsulation and controlled release [34]. In contrast, liposome drug delivery has low MICs. Moreover, some polymers such as chitosan have antibacterial characteristics, so it can act against biofilm forming bacteria [35].

Persister and intracellular microorganisms

Persisters are antibiotic-tolerant bacteria that are metabolically inactive cells due to its slow growth rate and can continue to grow after stress response. However, it is not mediated via mutation like others antibiotic tolerant bacteria [36]. Persisters stay at the site of infection during antibiotic therapy, but all pathogenic bacteria are eradicated. This contributes to the re-infection [37]. To overcome, liposome loaded with antibiotics are used since liposome can transport the antibiotics into the cells when attached to the cellular membrane [38].

Swarming phenomenon

Swarming is the locomotion of bacterial cells across membrane by changing into hyperflagellated, elongated and polynucleated cells. Bacteria move to the surface in desired direction using flagella during swarming [39]. However, swarming causes bacteria resistant to some antibiotics. To avoid antibiotic resistance, the swarmed cells are sub-cultured to convert them back to planktonic cells [40].

DISCUSSION

The use of nanoparticles as delivery vehicles for antimicrobial agents suggests a new and promising paradigm in the design of effective therapeutics against many pathogenic bacteria. This new invention will bring a lot of benefits to the health sector along with solving problems that are found in conventional antibiotics.

Table 1: Advantage and disadvantage of nanoantibiotics and conventional antibiotics

	Nanoantibiotics	Conventional antibiotics	References
Advantage	• Targeted delivery of drugs by specific accumulation • Lesser side effects of chemical antimicrobials • Low antimicrobial resistance • Controlled drug release • Prolong therapeutic effect by slow elimination • Wide therapeutic index • Better solubility • Low immunosuppression • Low cost	• Absence of nanomaterials in the body • Low systemic exposure to locally administrated drugs • Absence of nanotoxicity • Well-established characterization techniques	[14]
Disadvantage	• Nanotoxicity • High systemic exposure to locally administrated drugs • Intravenously injected nanomaterials in tissues and organs causes high accumulation • Lack of characterization techniques that are not affected by the properties of nanoantibiotics	• No specific accumulation • Many side effects of chemical antimicrobials • High antimicrobial resistance • Short half-life due to fast elimination • Usual pharmacokinetics of free drugs • Narrow therapeutic index • Sometimes poor solubility • Immunosuppression • High cost	[14]

Nanoantibiotics has many clinical advantages. Firstly, it can be activated by certain stimuli for targeted delivery [41]. This proves to be effective to treat abscess, which usually is acidic and lowers the potency of conventional therapy. Nanoantibiotics can also target infectious diseases by overcoming anatomic barriers due to its material and size [8]. Secondly, it can be modified for different Physico-chemical properties to reduce side effects made by conventional antibiotics [42] This can be achieved by increasing the solubility and stability [26]. Thirdly, it can overcome the resistance of bacteria towards conventional antibiotics. Nanoantibiotics also prolong drug circulation and improve therapeutic index. Many studies show greater efficacy of nanoantibiotics than conventional antibiotics [42]. Therefore, nanoantibiotics are very beneficial because of their great number of benefits compared to antimicrobial agents. The combinations of antibiotics with nanoparticles are exhibits the good synergistic effects against the microbes [43].

Even though nanoantibiotics provide a lot of benefits, there is a great challenge for it to overcome before clinical use globally. One of them is how will the nanoantibiotics interact with the body, which is required in order to calibrate does and deciding proper routes of administration for optimal therapeutic effects. Not only that, the toxicity of nanoantibiotics is also an issue before successful clinical translation [44]. Studies have observed that nanoantibiotics accumulates in the lungs, colon, liver, spleen, bone marrow and lymphatics if injected intravenously [45]. Nanoantibiotics that are inhaled can enter the circulatory system and reaching the liver, heart, lungs, brain and spleen [44]. The toxicity of nanoantibiotics toward humans is not certain currently, but it is believed that it shares the same nanotoxicity of other non-antibiotic nanomaterials. Research have suggested that using nanoantibiotics can cause nanotoxicity in many organs.

CONCLUSION

Antimicrobial resistance has become a serious threat towards human health. Pathogens have developed resistance to conventional antibiotics because of multiple drug resistance, reducing their effectiveness. Nanotechnology-based drug delivery systems for prospective nanoantibiotics are being developed in the twenty-first century to combat different drug-resistant diseases. Because of their high surface area to volume ratio and advantageous physicochemical features, nanoantibiotics are effective novel antibacterial agents. In comparison to traditional antibiotics, nanoantibiotics have improved absorption, dispersion, durability, and controlled release. As a result, nanoantibiotics are a viable option for reducing cytotoxicity and antibiotic resistance. Nanoantibiotics are also cost-effective and adaptive to a variety of drug resistance. However, further study is needed to determine if these new nanoantibiotics are effective and safe enough to combat numerous drug-resistant infections.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Simpkin VL, Renwick MJ, Kelly R, Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. J Antibiot (Tokyo).

2017;70(12):1087-96. doi: 10.1038/ja.2017.124. PMID 29089600.

2. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci USA. 2018;115(15):E3463-70. doi: 10.1073/pnas.1717295115, PMID 29581252.
3. Otaka E, Itoh T, Osawa S, Tanaka K, Tamaki M. Peptide analyses of a protein component, 50-8, of 50s ribosomal subunit from erythromycin-resistant mutants of Escherichia coli and Escherichia freudii. Mol Gen Genet. 1972;114(1):14-22. doi: 10.1007/BF00268742, PMID 4552494.
4. Piddock L, Garneau Tsodikova S, Garner C. Ask the experts: how to curb antibiotic resistance and plug the antibiotics gap? Future Med Chem. 2016;8(10):1027-32. doi: 10.4155/fmc-2014-0032, PMID 27327784.
5. Jamil B, Imran M. Factors pivotal for designing of nanoantimicrobials: an exposition. Crit Rev Microbiol. 2018;44(1):79-94. doi: 10.1080/1040841X.2017.1313813, PMID 28421881.
6. Dizaj SM, Lotfipour F, Barzegar Jalali M, Zarrintan MH, Adibkia K. Antimicrobial activity of the metals and metal oxide nanoparticles. Mater Sci Eng C Mater Biol Appl. 2014;44:278-84. doi: 10.1016/j.msec.2014.08.031, PMID 25280707.
7. Gold K, Slay B, Knackstedt M, Gaharwar AK. Antimicrobial activity of metal and metal-oxide-based nanoparticles. Adv Therap. 2018;1(3):6003-9. doi: 10.1002/adtp.201700033.
8. Lasemi E, Navi F, Lasemi R, Lasemi N. Complications of antibiotic therapy and introduction of nanoantibiotics a textbook of advanced. Oral Maxillofac Surg. 2016;3.
9. Li J, Xie B, Xia K, Li Y, Han J, Zhao C. Enhanced antibacterial activity of silver doped titanium dioxide-chitosan composites under visible light. Materials (Basel). 2018;11(8):1403. doi: 10.3390/ma11081403, PMID 30103430.
10. Karuppiah Chandran P, Pambayan Ulagan M. Antimicrobial and anticancer activity of silver nanoparticles from edible mushroom: a review. Asian J Pharm Clin Res. 2017;10(3):37-40. doi: 10.22159/ajpcr.2017.v10i3.16027.
11. Ovais M, Zia N, Khalil AT, Ayaz M, Khalil A, Ahmad I. Nanoantibiotics: recent developments and future prospects. Frontiers in Clinical Drug Research- Anti-Infectives. 2019;15:158-82. doi: 10.2174/9781681086378119050006.
12. Saif S, Tahir A, Chen Y. Green synthesis of iron nanoparticles and their environmental applications and implications. Nanomaterials (Basel). 2016;6(11):209. doi: 10.3390/nano6110209, PMID 28335338.
13. Pund S, Joshi A. Nanoarchitectures for neglected tropical protozoal diseases: challenges and state of the art. Nano Microscale Drug Deliv Syst Des Fabr. 2017:439-80.
14. Huh AJ, Kwon YJ. 'Nanoantibiotics': A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release. 2011;156(2):128-45. doi: 10.1016/j.jconrel.2011.07.002, PMID 21763369.
15. Dresselhaus MS, Dresselhaus G, Eklund PC, Rao AM. Carbon nanotubes BT-the physics of fullerene-based and fullerene-related materials. The Phys Fullerene-Based Fullerene Relat Mater. 2000:331-79.
16. Akhavan O, Ghaderi E. Toxicity of graphene and graphene oxide nanowalls against bacteria. ACS Nano. 2010;4(10):5731-6. doi: 10.1021/nn101390x, PMID 20925398.
17. Dasari Shareena TP, McShan D, Dasmahapatra AK, Tchounwou PB. A review on graphene-based nanomaterials in biomedical applications and risks in environment and health. Nanomicro Lett. 2018;10(3):53. doi: 10.1007/s40820-018-0206-4, PMID 30079344.
18. Sondi I, Salopek Sondi B. Silver nanoparticles as antimicrobial agent: A case study on E. coli as a model for gram-negative bacteria. J Colloid Interface Sci. 2004;275(1):177-82. doi: 10.1016/j.jcis.2004.02.012, PMID 15158396.
19. Joguparthi V, Anderson BD. Liposomal delivery of weak hydrophobic acids: enhancement of drug retention using a high intraliposomal pH. J Pharm Sci. 2008;97(1):433-54. doi: 10.1002/jps.21135, PMID 17918731.
20. Modi S, Anderson BD. Determination of drug release kinetics from nanoparticles: overcoming pitfalls of the dynamic dialysis method. Mol Pharm. 2013;10(8):3076-89. doi: 10.1021/mp400154a, PMID 23758289.
21. Sikwal DR, Kalhapure RS, Rambharose S, Vepuri S, Soliman M, Mocktar C, Govender T. Polyelectrolyte complex of vancomycin as a nanoantibiotic: preparation, *in vitro* and *in silico* studies. Mater Sci Eng C Mater Biol Appl. 2016;63:489-98. doi: 10.1016/j.msec.2016.03.019, PMID 27040243.
22. Lindner LH, Hossann M. Factors affecting drug release from liposomes. Curr Opin Drug Discov Devel. 2010;13(1):111-23. PMID 20047152.
23. Saidykhan L, Abu Bakar MZBA, Rukayadi Y, Kura AU, Latifah SY. Development of nanoantibiotic delivery system using cockle shell-derived aragonite nanoparticles for treatment of osteomyelitis. Int J Nanomedicine. 2016;11:661-73. doi: 10.2147/IJN.S95885, PMID 26929622.
24. Hussein Al-Ali SH, El Zowalaty ME, Hussein MZ, Ismail M, Webster TJ. Synthesis, characterization, controlled release, and antibacterial studies of a novel streptomycin chitosan magnetic nanoantibiotic. Int J Nanomedicine. 2014;9:549-57. doi: 10.2147/IJN.S53079, PMID 24549109.
25. Assali M, Zaid AN, Abdallah F, Almasri M, Khayyat R. Single-walled carbon nanotubes-ciprofloxacin nanoantibiotic: strategy to improve ciprofloxacin antibacterial activity. Int J Nanomedicine. 2017;12:6647-59. doi: 10.2147/IJN.S140625, PMID 28924348.
26. Duan F, Feng X, Jin Y, Liu D, Yang X, Zhou G, Liu D, Li Z, Liang XJ, Zhang J. Metal–carbenicillin framework-based nanoantibiotics with enhanced penetration and highly efficient inhibition of MRSA. Biomaterials. 2017;144:155-65. doi: 10.1016/j.biomaterials.2017.08.024, PMID 28834764.
27. Silhavy TJ, Kahne D, Walker S. The bacterial cell envelope. Cold Spring Harb Perspect Biol. 2010;2(5):a000414. doi: 10.1101/cshperspect.a000414, PMID 20452953.
28. Delcour AH. Biochimica et biophysica acta outer membrane permeability and antibiotic resistance. BBA Proteins Proteomics. 2009;5:808-16.
29. Hajipour MJ, Fromm KM, Ashkarran AA, Jimenez de Aberasturi D, de Larramendi IR, Rojo T, Serpooshan V, Parak WJ, Mahmoudi M. Antibacterial properties of nanoparticles. Trends Biotechnol. 2012;30(10):499-511. doi: 10.1016/j.tibtech.2012.06.004. PMID 22884769.
30. Gilbert P, Collier PJ, Brown MRW. Influence of growth rate on susceptibility to antimicrobial agents: biofilms, cell cycle, dormancy, and stringent response. Antimicrob Agents Chemother. 1990;34(10):1865-8. doi: 10.1128/AAC.34.10.1865, PMID 2291653.
31. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science. 1998;280(5361):295-8. doi: 10.1126/science.280.5361.295, PMID 9535661.
32. Smith AW. Biofilms and antibiotic therapy: is there a role for combating bacterial resistance by the use of novel drug delivery systems? Adv Drug Deliv Rev. 2005;57(10):1539-50. doi: 10.1016/j.addr.2005.04.007, PMID 15950314.
33. Hou J, Miao L, Wang C, Wang P, Ao Y, Qian J, Dai S. Inhibitory effects of zno nanoparticles on aerobic wastewater biofilms from oxygen concentration profiles determined by microelectrodes. J Hazard Mater. 2014;276:164-70. doi: 10.1016/j.jhazmat.2014.04.048, PMID 24880618.
34. Forier K, Raemdonck K, De Smedt SC, Demeester J, Coenye T, Braeckmans K. Lipid and polymer nanoparticles for drug delivery to bacterial biofilms. J Control Release. 2014;190:607-23. doi: 10.1016/j.jconrel.2014.03.055, PMID 24794896.
35. Wood TK, Knabel SJ, Kwan BW. Bacterial persister cell formation and dormancy. Appl Environ Microbiol. 2013;79(23):7116-21. doi: 10.1128/AEM.02636-13, PMID 24038684.
36. Bald D, Koul A. Advances and strategies in the discovery of new antibacterials for combating metabolically resting bacteria. Drug Discov Today. 2013;18(5-6):250-5. doi: 10.1016/j.drudis.2012.09.007, PMID 23032727.
37. Maurin M, Raoult D. Use of aminoglycosides in treatment of infections due to intracellular bacteria. Antimicrob Agents

Chemother. 2001;45(11):2977-86. doi: 10.1128/AAC.45.11.2977-2986.2001, PMID 11600345.

38. Oh YK, Nix DE, Straubinger RM. Formulation and efficacy of liposome-encapsulated antibiotics for therapy of intracellular Mycobacterium avium infection. Antimicrob Agents Chemother. 1995;39(9):2104-11. doi: 10.1128/AAC.39.9.2104, PMID 8540724.
39. Kearns DB. A field guide to bacterial swarming motility. Nat Rev Microbiol. 2010;8(9):634-44. doi: 10.1038/nrmicro2405, PMID 20694026.
40. Pelgrift RY, Friedman AJ. Nanotechnology as a therapeutic tool to combat microbial resistance. Adv Drug Deliv Rev. 2013;65(13-14):1803-15. doi: 10.1016/j.addr.2013.07.011, PMID 23892192.
41. Sandhiya S, Dkhar SA, Surendiran A. Emerging trends of nanomedicine-an overview. Fundam Clin Pharmacol. 2009;23(3):263-9. doi: 10.1111/j.1472-8206.2009.00692.x, PMID 19527298.
42. Hetrick EM, Shin JH, Stasko NA, Johnson CB, Wespe DA, Holmuhamedov E, Schoenfisch MH. Bactericidal efficacy of nitric oxide-releasing silica nanoparticles. ACS Nano. 2008;2(2):235-46. doi: 10.1021/nn700191f, PMID 19206623.
43. Gupta M. Inorganic nanoparticles: an alternative therapy to combat drug-resistant infections. Int J Pharm Pharm Sci. 2021;13(8):20-31. doi: 10.22159/ijpps.2021v13i8.42643.
44. El-Ansary A, Al-Daihan S. On the toxicity of therapeutically used nanoparticles: an overview. J Toxicol. 2009;2009:754810. doi: 10.1155/2009/754810.
45. Hagens WI, Oomen AG, de Jong WH, Cassee FR, Sips AJAM. What do we (need to) know about the kinetic properties of nanoparticles in the body? Regul Toxicol Pharmacol. 2007;49(3):217-29. doi: 10.1016/j.yrtph.2007.07.006, PMID 17868963.