International Journal of
Molecular Microbiology

Review Article 2023 | Volume 6 | Issue 1 | 1-23

Open Access
Article Information

Received: February 16, 2023

Accepted: February 21, 2023

Published: February 28, 2023

Keywords
Antibiotic,
Antibiotic Resistance,
Nanoparticles,
Nano-carriers,
Encapsulated Peptides.

How to cite
Khalid, U.A., Afolabi, B.L., Abdullahi, A., Attah, E.I., Toor, A.I., Saleem, R., Khan, S.J., Liaqat, A., 2023. Nano-Carriers Based Combating Approach against Antibiotic Resistance: An Insight into Nanoparticles Based Peptide Delivery. Int. J. Mol. Microbiol., 6(1): 1-23.

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Nano-Carriers Based Combating Approach against Antibiotic Resistance: An Insight into Nanoparticles Based Peptide Delivery

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Abstract:
Antibiotic resistance is the harbinger of a catastrophe for the globe in health point of view. Microbial resistances are emerging continuously and are causing life loss. Scientists and researchers are taking actions against this wildfire. Many medications and preventative strategies have been recommended to tackle this situation. In this regard, nanoparticles based medication came up with a new game plan. Nanoparticles are ideal due to their size, surface interaction, encapsulating drugs, targeted actions and stable delivery. Encapsulated peptide nanoparticles showed a new phase of drug delivery. Peptides are small sequences of amino acids, which upon delivery into the host cells proved to be fatal for resistant bacteria. These peptides can be the good candidate for medication and can be the alternative of antibiotics. However, natural peptides have some flaws regarding efficient actions; scientists are looking for synthetic peptides. Few studies have been conducted in this regard. This article focuses on the comprehensive review of antibiotic resistance and nano-carriers based therapy, which could be the ray of hope for the scientists against microbial resistance.

INTRODUCTION

Before the advent of antibiotics, humans have been using different substances such as plants, bread, mold, and honey to treat infections over the years (Molan, 2001). The use of antibiotics can be dated back to the early 20th century when Arsphenamine was reportedly discovered by Paul Ehrlich and Sahachirō Hata for the effective treatment of syphilis (Kapp, 2018). Prontosil is the second antibiotic to be discovered after arsphenamine by Gerhard Domagk and his team (Bentley, 2009) on rigorous experimentation of dye's action on bacteria. Penicillin, as Sulphonamide, was introduced into the market in 1940 after its discovery in 1928 by Alexander Fleming (Ligon, 2004).

In subsequent decades, other new antibiotics that went into clinical use were discovered from fungi, bacteria, and plant materials. However, the discovery of new antibiotics has not been possible since the late 20th century amidst the prevailing antimicrobial resistance (Rossiter *et al.,* 2017).

Antibiotics produce therapeutic activity by either preventing growth or killing the pathogens (Ling *et al.,* 2015). Trimethoprim, sulfamethoxazole, and fluoroquinolones inhibit microbial action by interfering with DNA synthesis. However, Trimethoprim and Sulfamethoxazole both being sulfonamide antibiotics, block the activity of enzymes that are involved in the synthesis of folic acid which is vital in the synthesis of DNA bases by bacteria Fluoroquinolones inhibits the replication of DNA by binding to the enzyme (Greenberg *et al.,* 2011). Some antibiotics elicit therapeutic activity by damaging or preventing the growth and repair of the bacterial cell wall and membrane (Cao *et al.,* 2002). Penicillin, cephalosporins, and carbapenems are all β-lactams antibiotics that inhibit the growth or kill bacteria by binding to a bacterial enzyme called penicillin-binding proteins (PBP) which is useful in building and repairing cell wall (Kishida *et al.,* 2006). So also Vancomycin which is a glycopeptide antibiotic in a likewise manner inhibits peptidoglycan synthesis and thus inhibits the formation of the cell wall (Hammes *et al.,* 1974). Aside from inhibition of cell wall, membrane, and DNA synthesis, some class of antibiotics inhibits the production of RNA (Lalaouna *et al.,* 2014). For example, Rifampicin, a vital antibiotic for the treatment of tuberculosis inhibits the production of RNA by binding to RNA polymerase which copies DNA into RNA (Campbell *et al.,* 2001). Many other antibiotics act by binding to parts of the bacterial ribosome, blocking its activity some of which include aminoglycosides, tetracyclines, macrolides, phenicols, and lincosamides (Wilson, 2014). Notwithstanding there are still other antibiotics whose therapeutic mechanism is yet unknown (Miller *et al.,* 2014).

Regrettably and unnecessary use of antibiotics has only increased the rate of antibiotic resistance in our communities and around the world (Hou *et al*., 2023). Antibiotics presently appear to be used not only in excess but also improperly and accounts for 20% to 50 % of all antibiotics used. However, nearly all the classes of antibiotics had one bacteria or the other that developed resistance (Crouch *et al.,* 2015). The resistance of microbes against the inhibiting action of antibiotics is majorly a result of intrinsic nature and mutation for both microbial and host cells (Coculescu, 2009).

Uses of Antibiotics

Antibiotics have been successfully used in serving as medicines and alternative medicines in various disease treatments (Nahar *et al.,* 2020). Salinomycin is used to treat cancer stem cells (Wang, 2011), while Gemifloxacin possesses known metastatic activity (Yadav and Talwar, 2019). Antibiotics are also used in perioperative antibiotic prophylaxis (Dinsmoor *et al.,* 2009). For example, Cefazolin was allegedly reported about thirteen years ago to be the widely recommended antibiotics among Canadian surgeons, while Vancomycin and Cefuroxine are also prescribed (de Beer *et al.,* 2009). Ceftriaxone is one of the drugs that constitute the regimen for gonorrhea patients (Schumacher and Ghanem, 2013). Flucloxacillin and aminoglycoside are also used for infections associated with preterm birth (Fernando *et al.,* 2008). Sulphamethoxypyridazine and chloramphenicol have been widely used for the

treatment of infections arising from complicated childbirth (Bonet *et al.,* 2017). Moreover, antibiotics are also widely used in livestock farming in the treatment of animal microbial diseases among others (Van *et al.,* 2020).

Antibiotic Resistance

The term resistance to bacteria is defined as bacteria that are not inhibited by the usually achievable systemic concentration of an agent with a normal dosage schedule and/or fall in the minimum inhibitory concentration ranges (Tripathti, 2003). Antibiotic resistance occurs when a bacteria or other microorganism can resist the effects of a particular antibiotic (Bisht *et al.,* 2009). Likewise, multiple drug resistance occurs when bacteria were able to show resistance to two or more drugs or drug classes. Acquiring resistance to one antibiotic with resistance to another antibiotic, to which the organism has not been introduced, is referred to as cross-resistance (Tripathi, 2003). Most bacteria acquire resistance to an antibiotic in such a way that reduces or eliminates the efficacy of drugs, chemicals, or other agents designed to kill them or prevent the infection. Thus the bacteria continue to survive thereby causing more harm (Bisht *et al.,* 2009).

Evolution of Antibiotic resistance

The development of different classes and generations of antibiotics coupled with overuse, misuse, and underuse of antibiotics is what triggers the evolvement of antibiotic-resistant microbes and their distribution in microbial populations throughout the world (Davies and Davieas, 2010). The development of antibiotic resistance was first reported in animal models in the 1940s (Frisch *et al.,* 1943) and subjectively reported among human patients in the 1970s (Cates *et al.,* 1978).

Different mechanisms of antibiotics have been reported over years but notwithstanding antibiotic resistances are still on the rising side. For example, the discovery of a bacterial penicillinase has revealed that most bacteria render penicillin non-effective. More also, a new spectrum of lactamase first enzyme found to hydrolyze expanded spectrum cephalosporins at a clinically significant level was acquired from environmental *Kluyvera* strains (causing soft tissue infection) and has been revealed in the clinic in the 1990s (Livermore *et al.,* 2007). So also streptomycin, produce in early 1944 for the treatment of tuberculosis, the mutant strains of *Mycobacterium tuberculosis* resistant to therapeutic concentrations of the antibiotic were found to have evolved during patient treatment. As some other antibiotics have been discovered and introduced into clinical practice for the treatment of tuberculosis, a similar course of events has been reported. While many workers understand antibiotic resistance as a recently acquired microbial character, studies on ancient DNA have revealed genes with resistance to β-Lactams, tetracycline, and glycopeptide antibiotics (D'Costa *et al.,* 2011).

The genetically transferable antibiotic resistance was reported in Japan in the mid-1950s (Davies, 1995) which has revolutionized the whole picture by introducing a genetical concept, that collections of antibiotic resistance genes could be spread by bacterial conjugation throughout an entire population of bacterial pathogens. However, it was recently in the past few years it has been appreciated that gene exchange is a property of bacteria that have occurred throughout the history of microbial evolution. The discovery of the presence of bacterial genomic sequences in eukaryotic genomes has offered a highlight and creates awareness of the great importance of horizontal gene transfer (HGT) in genome evolution. So also, other forms of transfer of genetic materials have been explored by the identification and distribution of gene sequences with genes for pathogenicity and other functional gene families in different bacterial species (Davies and Davies, 2010).

Moreover, plasmid-mediated transfer of antibiotic resistance has been reported and still under investigation because of its medical and, more recently, practical importance (Norman *et al.,* 2009). Macrolides and sister antibiotics such as erythromycin exert an effect by binding at different sites in the peptide exit end of the 50S ribosome subunit (Davies and Davies, 2010).

Factors Involved in Antibiotic Resistance

Antimicrobial resistance has an intense impact on the community and hospital-acquired infections in developing as well as developed countries. Certain factors are responsible for the resistance development, which range from genetic and epigenetics to environmental. One interesting fact is that human errors are one of the significant factors contributing to resistance development, such as incomplete antibiotic course, misuse of antibiotics, as well as over prescription of antibiotics (Alos, 2015). A few among these are discussed below:

Bacterial adaptation to antibiotic resistance

Acquiring a bacterial infection and then treating it with antibiotics is not a simple and straight forward process. Initially, bacterial infections are treated with antibiotics effectively, but the constant use of antibiotics has an impact on the bacterial genome. Also, bacteria show great susceptibility against antibiotics, but misuse in some ways has led to the genetic alteration in the bacterial genome, which favors resistance (Normark and Normark, 2002). New bacterial generations are evolving with selectively show resistance. The main resistance determining factor is the spontaneous mutations which act as a protective shield. Non-resistant bacteria in conjugation with resistance bacteria undergo a transfer of exogenous antibiotic resistance gene. Gene transfer enables the bacteria to survive under harsh conditions of antibiotics and soon there is a population of resistant bacteria. Human microbial flora is a combination of bacteria that are both susceptible and resistant bacteria and the levels of both types of bacterial populations are kept at balance (Andersson and Hughes, 2010 ; Larsson and Flach, 2022). Over-populated resistant bacteria start to flourish at a rapid rate depicting that genetic factors in combination with environmental conditions are responsible for the widespread issues of antibiotic resistance (Collins, 2008).

Poor prescription and Patients not finishing the entire antibiotic course

As earlier mentioned, the misuse and over-use of antimicrobial agent lead to the development of resistance (Barber *et al.,* 2017). However, antibiotics cannot be used randomly but with precise prescription as WHO has already warned about the “post-antibiotic era” (PAE). PAE is defined as the era where the antibiotics will no longer be able to kill the microbes with efficacy. Poor prescription is among the main reason. One area of excessive use of antibiotics is in dental practice. Antibiotics are excessively used in dental practices and the prescription is based upon the general clinical and bacteriological epidemiological factors. Such prescriptions are usually for a short period with the use of broad-spectrum antibiotics for a narrow range of infections (Oberoi *et al.,* 2015). Resistance is developing and is resulting in the fact that bacteria are not responsive to a wide range of commonly used antibiotics. Eradication of bacterial infection is not only dependent upon the relevant selection of antibiotics but also upon the completion of the antibiotic course to prevent the recurrence of infection. Doctors can make a big difference by prescribing the best-suited drug at standard doses and only in conditions when there are higher chances of systemic spread of bacterial infection. Data suggests that about 30% of issues of antibiotic resistance are the result of a poor choice of medicine, incomplete antibiotic course, and poor medical prescription (Asante *et al.,* 2017). Though antibiotic usage has its benefits, however the use of incorrectly or wrongly prescribed drug has led the scientist to think about the benefits-harms ratio. Genetic alterations such as the altered gene expression levels and induction of mutations are common methods to acquire resistance. An overall increased level of mutations at genetic and epigenetic levels leads to disturbed microbial activity and enhanced survival as well as the dominance of resistant bacteria (Viswanathan, 2014).

Poor infection control in health care settings

In Clinical settings, unnecessary intake of antibiotics and less control on infection spread can lead to the development of drug resistance. For example, people can get hospital-acquired infections when they are under medical care which can lead to sepsis or even death. Most of the hospital-acquired infections are caused by

antibiotic-resistant bacteria. The pathogens responsible for these infections can spread and transmit between the patients through improper health care facilities. So, these hospital-acquired infections become a major and non-preventable threat to the safety of the patients (Hughes, 2008). A little progress has been made to stop these infections but still, more work is needed to prevent their spread between the patients. One of the major ways to stop antibiotic resistance in bacteria is by stopping inappropriate use of antibiotics and through this way, the paramount microbial threat of the 21st century can be controlled (Collins, 2008).

Absence of new antibiotics being discovered

Resistance development in bacteria is not only a matter of concern for humans but also in animals and environment as well. All this is caused by the evolving superbugs. Multidrug resistance is increasing at rapid rate with no long term protective strategy at disposal (Aslam *et al.,* 2018). While the bacteria are acquiring resistance at greater speed, there is no much development of new antibiotics as for the last about 50 years there was the development of only 1 class of antibiotics has developed termed as daptomycin (Lewis, 2013).

Reasons for the absence of new antibiotics being discovered is the lack of collaboration between research institutes and investment agencies. Need of the hour is to realize that antibiotic resistance is not solely a genetic phenomenon occurring due to spontaneous mutations but also of environmental factors among which the human errors and misuses are at the top of the list.

The Role of Nanoparticles to Overcome Antibiotic Resistance

Nanotechnology is a fast-growing technology that provides an avenue for the synthesis of small scale particles (1–100 nm) called nanoparticles (Rai *et al.,* 2012; Singh *et al.,* 2020). Due to their unique size, shape, a large surface to volume ratio, and easy manipulative properties, they have been successfully investigated in different areas of medicine such as drug delivery and therapeutics, diagnosing, and tissue repair commonly referred to as nanomedicine (Gupta *et al.,* 2019a; Singh *et al.,* 2020). The advancement of nanotechnology has now focused more on the use of different nanoparticles to target antimicrobial resistance (Gupta *et al.,* 2019a). Antimicrobial resistance is a global challenge and despite all energy driven to combat it, it is still on the rising side (Hajipour *et al.,* 2012; Smerkova *et al.,* 2020). Recently Centers for Disease Control and Prevention (CDC) in the United States stated that over 2.8 million and 35, 000 people were infected and die respectively due to antimicrobial resistance (AMR) (CDC, 2019). However, surface functionalization of nanoparticles for ligand immobilization and encapsulation of therapeutic agents have proven to be efficient in the disruption of AMR (Gupta *et al.,* 2016; Gupta *et al.,* 2019a). Nanoparticles can penetrate the microbe's cell wall, destroying cell organelles thereby causing apoptosis/cell death (Arakha *et al.,* 2015). They function mainly by the disruption of the cell wall, causing oxidative stress, enzyme inactivation, and interfering with protein/DNA function (Arakha *et al.,* 2015; Cheng *et al.,* 2016).

Bacterial confer resistance by the alteration in the target sites of antibiotics but nanoparticles/nano-coupled antibiotics overcome this mechanism of resistance by multiple bactericidal pathways. Most nanomaterials are engineered and synthesized to restrain specific antimicrobial resistance although irrespective of the type of nanomaterial, their peculiar physiochemical parameter allows them to effectively bind and disintegrate the bacterial membrane resulting in cytoplasmic leakage. They are usually coupled with antibodies, protein, a peptide, CRISPR-Cas system, and/or siRNAs as shown in Figure 1 for effective targeting and to enhance antibacterial activity (Smerkova *et al.,* 2020). Upon entrance into the bacterial cell, they exhibit toxicity by interfering with DNA/Protein expression, initiation of oxidative stress, and cell death. Numerous nanoparticles have been synthesis to overcome the antibacterial resistance of *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Yersinia pestis*, *Escherichia coli*, *Salmonella aureus,* and *Acinetobacter*

baumannii to mention a few (Leid *et al.,* 2012; Rai *et al.,* 2012; Huang *et al.,* 2016; Sajjadi *et al.,* 2020).

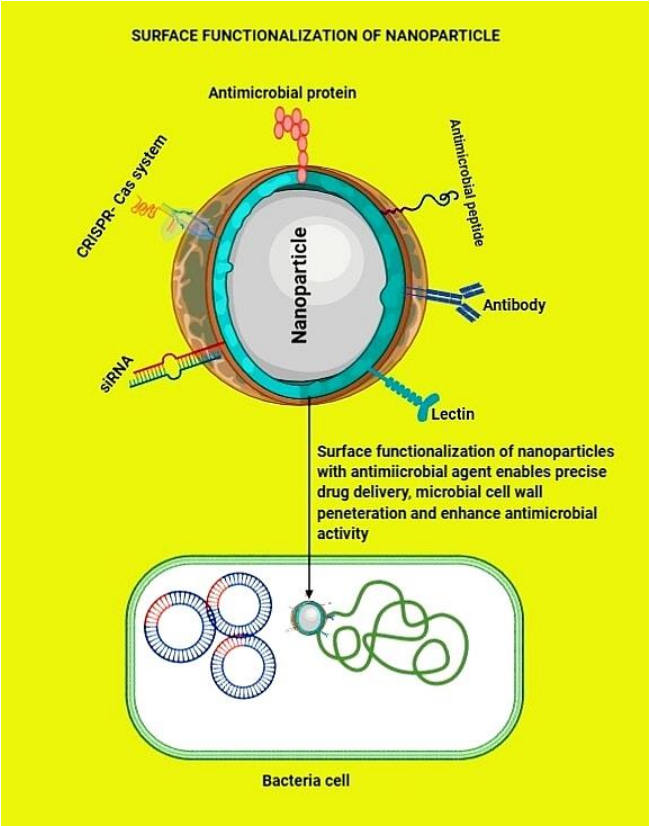

Fig. 1. Surface functionalization of nanoparticle for cell penetration, specific and active targeting.

Nanoparticles play an important role to overcome antibiotic resistance, they cause oxidative stress, release of metal ion, and they exhibit other non-oxidative mechanisms (resulting in disruption of enzyme activity, DNA damage, cytoplasmic release, distorted structure, disruption of the cell wall, plasmid damage, and the interruption of electron transport) as shown in Figure 2 (Hemeg, 2017; Zaidi *et al.,* 2017; Lee *et al.,* 2019).

Role of Oxidative Damage

The major mechanism of nanoparticle toxicity and antibacterial activity has been linked with oxidative damage via the generation of reactive oxygen species (H_2O_2, O_2^-, O_2, and ·OH). Different reactive oxygen species are produced by the reduction of molecular oxygen in the microenvironment of bacteria. The reactive oxygen species produced depends on the nature of the nanoparticles, for example, Mg and Ca nanoparticles will generate superoxide radical (Lellouche *et al.,* 2012) and Zinc oxide (Sirelkhatim *et al.,* 2015), and Titanium dioxide (Wong *et al.,* 2015) nanoparticles can generate hydroxyl radical and hydrogen peroxide. However, a nanoparticle can generate all the mentioned ROS (Zaidi *et al.,* 2017). The ROS generated causes oxidative damage by altering DNA replication and protein synthesis, damages cell membrane, and interferes with membrane permeability via lipid peroxidation (Wang *et al.,* 2017). The antibacterial activity of many nanoparticles causes cell death and apoptosis by oxidation of proteins and their oxidative attack on key enzymes (Wu *et al.,* 2011).

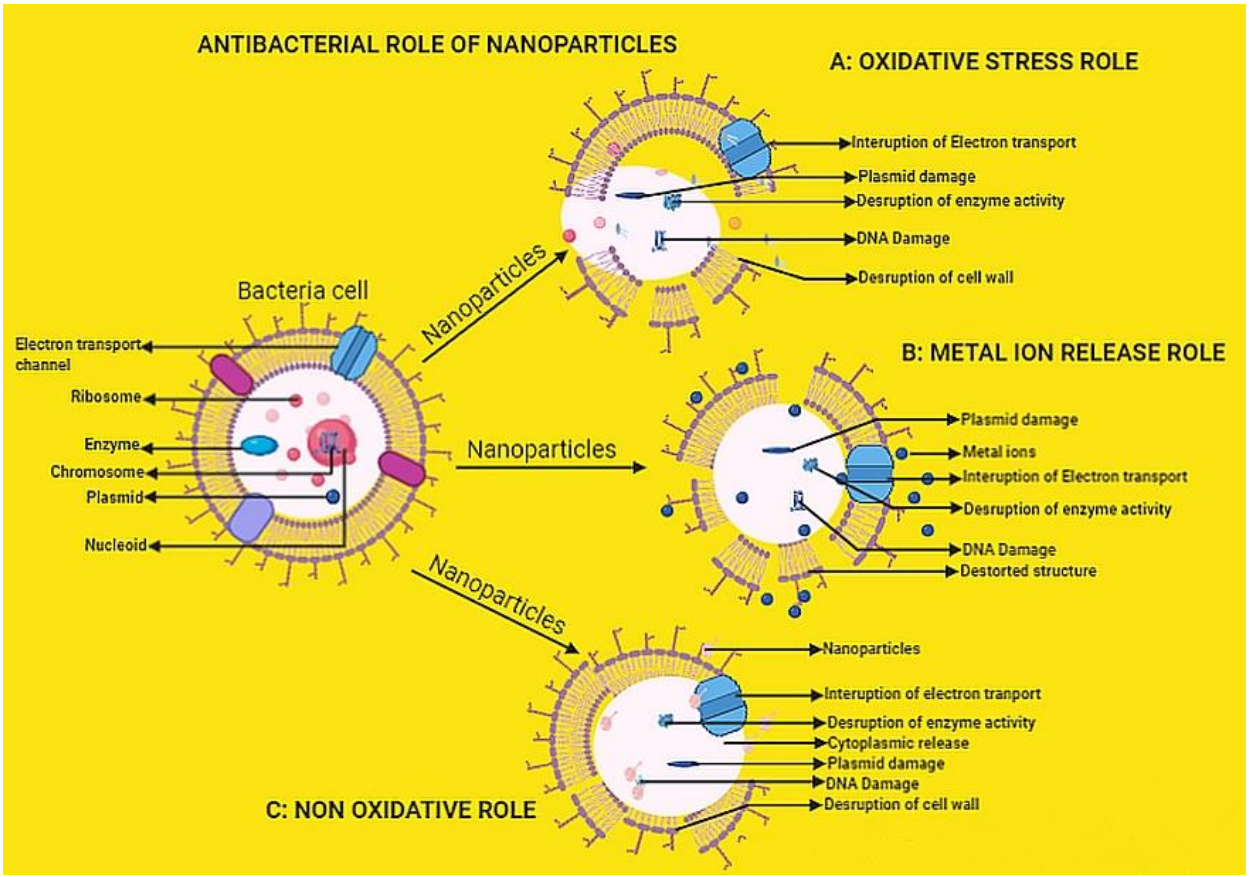

Fig. 2. Schematic portray of nanoparticles and their antibacterial role. A: Oxidative stress role. B: Metal ion release role. C: Non oxidative role.

Role of metal ion release

Metallic based nanoparticles release metal ions that can interact with the carboxyl, amino and mercapto groups on the bacterial cell membrane. Microbes are highly sensitive to metal ions although their interaction with metal ions varies with microorganisms (Hemeg, 2017). Their interaction with the membrane protein and nucleic acid interfere with bacterial physiological reactions and disrupt the cell morphology via proton leakage (Losasso *et al.,* 2014; Yu *et al.,* 2014). Zinc and silver nanoparticles enhance their antibacterial activity by the release of Zn^{2+} and Ag^{+} respectively (Franci *et al.,* 2015; Dakal *et al.,* 2016; Durán *et al.,* 2016). Also, cupric nanoparticles release Cu^{2+} on *the Bacillus subtilis* cell membrane which interacts with the amino and carboxyl group of the membrane (Yoon *et al.,* 2007). The release of metal ions by metallic nanoparticles is not the main mechanism by which they confer antibacterial activity, but it however contributes to their activity against antimicrobial resistance (Losasso *et al.,* 2014).

Other non-oxidative roles

Nanoparticles also exhibit microbial toxicity via non-oxidative interaction with the cell wall and the cell membrane. Nanoparticles' first-line action is to penetrate the microbial cell wall via interacting with the bacteria lipopolysaccharides and phospholipids defense barrier (Lesniak *et al.,* 2013). Due to the non-porous nature of gram-negative bacteria, they are more resistant to nanoparticle penetration (Zaidi *et al.,* 2017). The interaction of some nanoparticles with lipopolysaccharides (-) enables permeability and dissipation of the proton gradient of the cell membrane (Pelgrift and Friedman, 2013). Once nanoparticles gain entrance into the bacterial

cell, they interfere with protein and DNA synthesis through multiple cascade oxidative reactions. Silver (Pelgrift and Friedman, 2013), Cupper (Chatterjee *et al.,* 2014), Titanium (Joost *et al.,* 2015), Gold (Huo *et al.,* 2016), and Nickel (Khashan *et al.,* 2016) nanoparticles cause' cell lysis by disruption of cellular transport and respiratory chain.

Nano-carriers based approach via Antimicrobial peptides (AMPs)

Given the current situation of microbial resistance, antibiotic based therapeutic strategies are getting ineffective. Due to which, the demand for new and effective therapeutic approach has increased (Czaplewski *et al.,* 2016). Researchers are looking for that approach which could fix the flaws of previous therapeutics attempt (Bush *et al.,* 2011). In this regard, antimicrobial peptides (AMPs) came up with a new game plan to tackle antibiotic resistance (Czaplewski *et al.,* 2016 ; Erdem and Kesmen, 2022). AMPs are amino acid sequences that vary in number and arrangements, found in various biological entities. Discover history of AMPs is about 70 years and proved to be resistance against some microbial communities (Biswaro *et al.,* 2018). Structurally, AMPs consist of 5-50 amino acid chains, most of which have a secondary structure with L-amino acids (Sirtori *et al.,* 2008). By 2013, the number of AMPs discovered had reached 5,000 (Bahar and Ren, 2013). AMPs are prominent with immunomodulator characteristics which make them special as a novel therapeutic candidate. Some of them are in clinical trials and practice (Fjell *et al.,* 2012; Fox, 2013).

When it comes to the mechanism of action, it has not been clearly decided yet. However, many experimental attempts gave the clue of interaction of AMPs with the intracellular and extracellular membrane in the models. Attachment of AMPs to the membrane depends on several factors i.e. sequence arrangements of the amino acid, charge, and hydrophobic nature. Many reported studies indicated that the interaction of AMPs with the phospholipid membrane of microbes is mainly due to their biochemical nature (Scocchi *et al.,* 2016). Along with membrane interaction, AMPs make their way to destabilize the microbial membrane, via making pores into the phospholipid membrane (Lee *et al.,* 2010).

In addition to the profitable use of AMPs, some undesirable challenges also exist there. Low yield is the major concern with contaminated impurities, during isolating peptides (Diehnelt, 2013). Other unwanted characteristics include; while deactivating bacteria, AMPs could be fatal to eukaryotic cells too, and peptides may prone to bacterial protease enzyme which may lead to proteolysis (Navon-Venezia *et al.,* 2002; Schmidtchen *et al.,* 2002). To get rid of these undesirable characteristics, scientists are in search of the production of synthetic peptides and several studies on these are in progress (Diehnelt, 2013). The positive aspects of synthetic peptides are, to be potent, by arranging amino acid sequences in a way that these could prove to be effectively resistant (Riedl *et al.,* 2011). But in both cases, i.e. natural and synthetic peptides, these are not so cost-effective as compared to antibiotics (Otvos and Wade, 2014).

Several drug delivery methods are in practice which can effectively encapsulate the drugs and biomolecules (Torchilin, 2006). Nanotechnology is considered to be one of the delivery systems which can easily deliver drugs, proteins, and other biomolecules to specific targets (Biswaro *et al.,* 2018). To overcome the unwanted and offensive characteristics of AMPs, nanotechnology is proved to an efficient strategy (Umerska *et al.,* 2017). Edges of nano-system are;

a. That peptides can be delivered safely without any change in nature

b. Nano carriers can deliver drugs and other molecules, by providing safety from external environment.

c. Targeted activity (Sadat *et al.,* 2016).

Storm et al. (1995) described the methodology of AMPs's delivery via nanotechnology approach. AMPs can be encapsulated in nano-

carriers and delivered in two ways i.e. Non directed delivery and directed delivery.

Non directed approach is the copy of typical, conventional delivery system in which no extra modifications or alterations are required in nano-carriers and this strategy is also called passive delivery (Storm *et al.,* 1995). In contrast, a directed attempt involves the modifications. This system is an efficient, reliable, and targeted one. Targeted delivery can be achieved by modifying the outer surface of nano-carriers with moieties and ligands (Lamprecht *et al.,* 2001). A passive system is a much easier one with limited agents involved. However, merits and demerits still exist there in both delivery systems (Hunter *et al.,* 2012; Solaro *et al.,* 2010). The illustrated view of the passive and active delivery system is shown in Figure 3 and Figure 4, respectively.

Nonetheless, it's the beginning phase of nanotechnology in delivering AMPs but still, safe encapsulating of peptides in nanoparticles is a challenging one (Biswaro *et al.,* 2018). There might be the possibility of interaction of encapsulated peptides with the inner surface of the nanomaterial, which may lead to the formation of pores and release of peptides (Mohammadi-Samani and Taghipour, 2014). Still, not even a single synthetic AMPs that are commercialized or even approved by the FDA (Molchanova *et al.,* 2017). Safety of health is also a great concern while using drug delivery carriers (Otvos and Wade, 2014). Some drug delivery systems operate on high or low temperature, which may disturb the chemistry of peptides (Gallarate *et al.,* 2011). Despite various challenges, vast research is on its way in encapsulation, safe delivery, and efficient use and choice of nano-carriers. Wide research could fill the gaps and can bring an efficient drug delivery system at the end (Biswaro *et al.,* 2018).

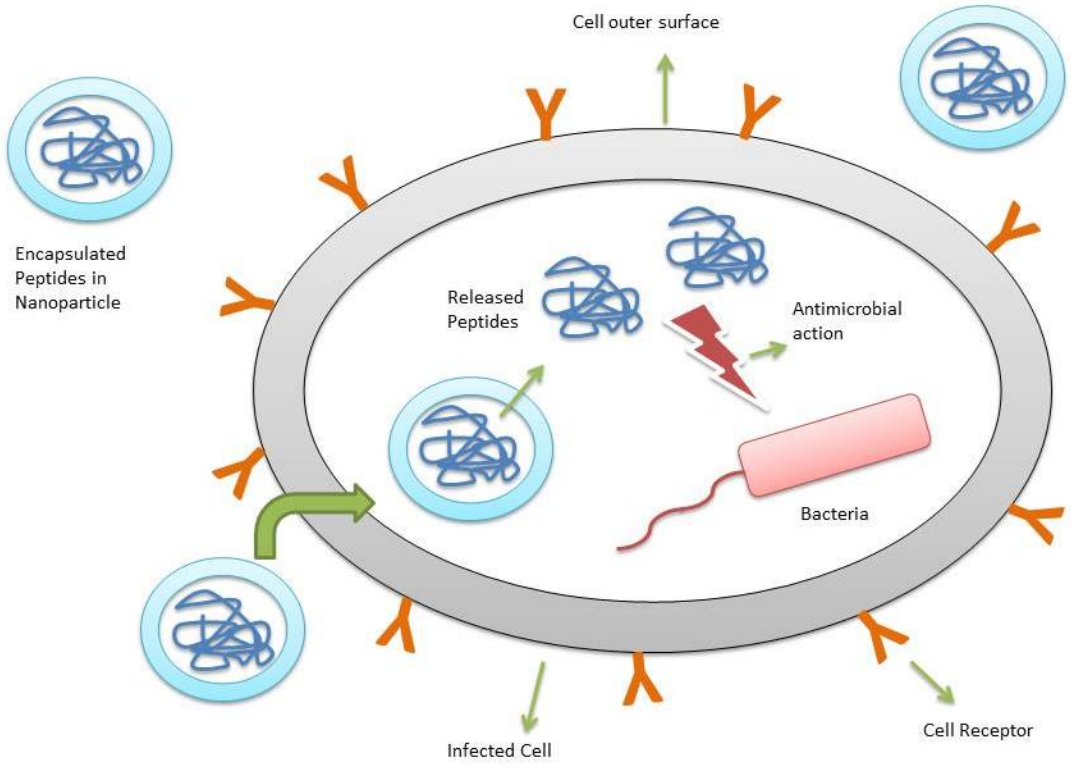

Fig. 3. This illustration represents the passive delivery of nanoparticles. In this passive system, nanoparticle-containing peptides are entered into the cell and do action against bacteria. No modification is involved in nanoparticles. Adapted with permission from Biswaro et al. (2018).

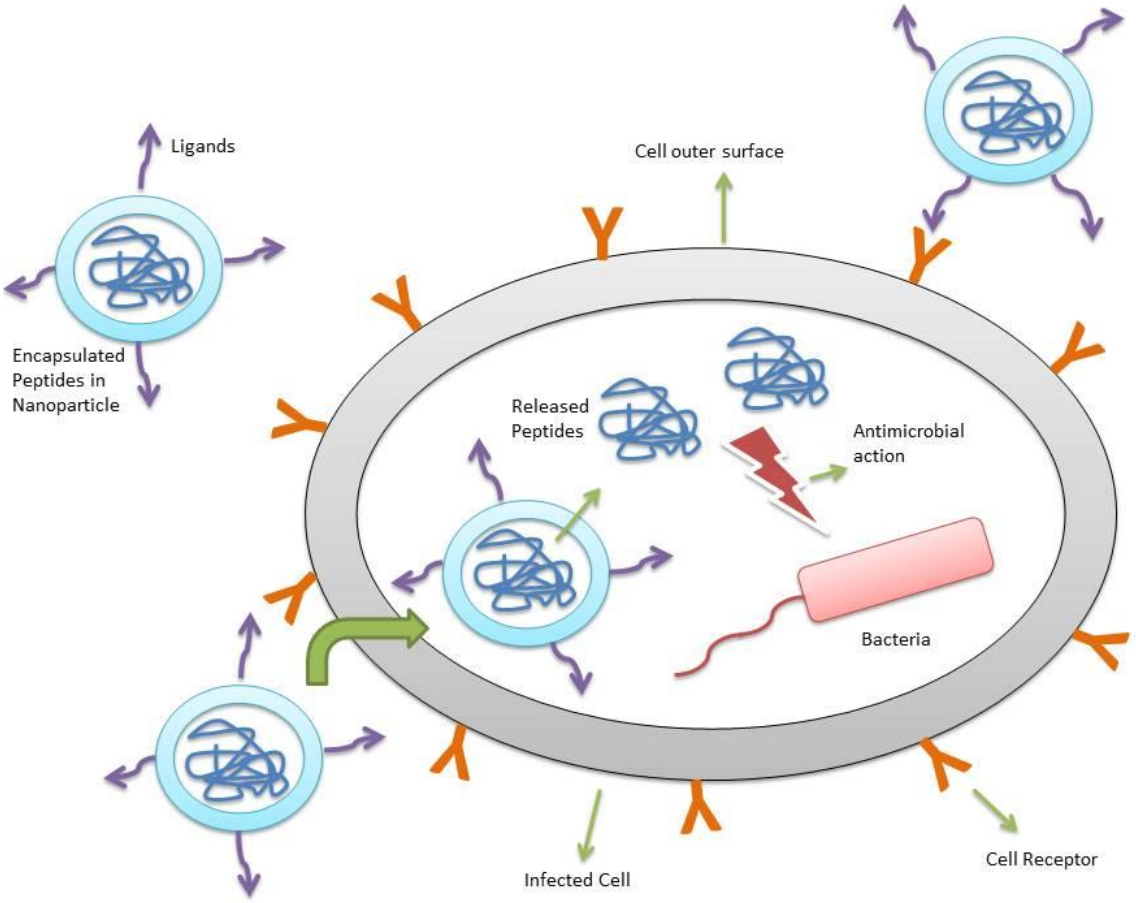

Fig. 4. This illustration represents the active delivery of nanoparticles. In this active system, ligands are available on the outer surface of nanoparticles, which help them to interact with the receptors of the cell, resulting in targeted entrance and delivery of encapsulated peptides. Adapted with permission from Biswaro et al. (2018).

Potentials of Nanoparticle Based Therapy

Nanotechnology offers many advantages in different fields of science (Yetisgin *et al.,* 2020). Nanoparticles are the keystones in the development blocks of nanotechnology. Recent advances in nanotechnology have shown that nanoparticles have great potential in every field. In recent years, billions of dollars have been invested worldwide in the field of NPs (Bamrungsap *et al.,* 2012). About 76% of nanotechnology research publications in 2014 are in the area of drug delivery systems (James *et al.,* 2014). The advantage of NP formulations is that they enhance the efficacy of treatment and reduce side effects thanks to their specific targeting action. During the last decade, nanoparticle-based formulations were developed to improve the drug delivery system (Prasad *et al.,* 2018).

This targeting depends on the composition of NPs themselves as well as their physical and chemical characteristics. In 1978 the first NP system was liposome developed as a drug carrier (Bonventre and Gregoriadis, 1978) and since then a large number of nanoparticles have been developed as delivery systems. Nanotechnology applications in drug delivery have the potential to transform the current situation of various diseases like cancer,

diabetes, infection, neurodegenerative diseases, and blood disorders into a whole new level (Petros and DeSimone, 2010).

Nanoparticles provide a better approach to alter and improve the pharmacokinetic and pharmacodynamic properties of different drug molecules. These nanoparticle-based therapies are used to improve therapeutic efficacy and reduce side effects in 'nano-pharmacology'. The delivery of therapeutic and diagnostic agents is greatly impacted by the potential medical and pharmaceutical benefits of nano-pharmacology (Jain *et al.,* 2014).

Despite the rapid improvement of strategies to fight cancer, cancer is still one of the leading causes of death worldwide. During the last 10 years the novel antineoplastic compounds, acting through induction of apoptosis, dysfunction in the cell cycle, gene transcription, and inhibition of angiogenesis process, have been presented (Sikora, 2002). The meteoric evolution of nanotechnology provides alternative approaches to overcome several limitations of conventional anti-cancer therapy (Piktel *et al.,* 2016). A new standard in novel anti-cancer methods in drug targeting functionalized nanoparticles is used to advance their transport to the dedicated site. Current nanotechnology allows for the simultaneous delivery of synergistic drug combinations and the engagement of the patient's innate and adaptive immune systems to combat cancer (Jia *et al.,* 2017). By designing NPs based on active targeting of immune cells, solid tumors, and the tumor microenvironment, higher effectiveness can be achieved. The application of nanotechnology to cancer immunotherapy holds greater promise for cancer patients in the future (Yan *et al.,* 2019).

Nano formulations play an important role in improving the healthcare sector. Many nano-therapeutic products are available in the market for parenteral administration, while several being meant for oral administration. One of the revolutionary products in this regard is glyconanopartcilces. The glyconanoparticle (GlycoNP) has various effects and plays a major role in the applications of drug delivery and bio imaging. It not only has the advantages of nano-drug delivery system but also utilizes the characteristics of multivalent interaction of sugar, which greatly improves the targeting of drug delivery (Zhang *et al.,* 2018). The GlycoNP have been widely used in biomarkers and biomedicines. GlycoNPs are easy to prepare and have unique physical, chemical, and biological properties having diverse applications in drug delivery and biomedical imaging (García *et al.,* 2010).

Brain disorders represent more than one-third of the total burden of diseases in Europe, where about a quarter of the population is affected (Jonssen, 2005). Nanoparticles provide a platform to construct hybrid drug delivery systems with revolutionizing the treatment of brain diseases. The potential mechanism of nanoparticle-mediated drug delivery across the BBB is determined by the chemistry, architecture, and properties of the nanoparticles (Barbu *et al.,* 2009; Saraiva *et al.,* 2016).

Nanoparticles plays important role in regenerative medicine such as nanoparticles-based MRI. The advantages of nanoparticle MRI over other tracking methods are numerous: it allows high-resolution, a non-invasive investigation into the effectiveness of stem cell therapies (Edmudson *et al.,* 2013). Nanoparticles have potential in the treatment of Tuberculosis. Their major advantages are the improvement of drug bioavailability and reduction of the dosing frequency making them more practical and affordable for treatment (Gelperina *et al.,* 2005).

Nano-particles and their likely use in antibacterial photodynamic treatment are one of the numerous ways nano-molecule assumes its job. Photodynamic treatment (PDT) has been foreseen as another framework to inactivate microorganisms as it doesn't prompt the determination of freak safe strains; a conspicuous advantage over anti-microbial treatment. PDT is considered a focal point for nanotechnology as the quality of the treatment can be extraordinarily improved by the utilization of nano-particles (Perni *et al.,* 2011). List of potentials of nanomaterials to biology are:

Fluorescent biological labels (Bruchez *et al.,* 1998; Chan and Nie, 1998; Wang *et al.,* 2002), Drug and gene delivery (Mah *et al.,* 2000; Panatarotto *et al.,* 2003), Bio detection of pathogens (Edelstein *et al.,* 2000), Detection of proteins (Nam *et al.,* 2003), Probing of DNA structure (Mahtab *et al.,* 1995), Tissue engineering (De *et al.,* 2003; Ma *et al.,* 2003), Tumor destruction via heating (hyperthermia) (Yoshida and Kobayashi, 1999), Separation and purification of biological molecules and cells (Molday and MacKenzie, 1982), MRI contrast enhancement (Weissleder *et al.,* 1990), and Phagokinetic studies (Parak *et al.,* 2002).

Limitations of Nano Therapies

In the last two decades, we have seen a surge in the use of nanotechnology-based products and therapies such as antimicrobial therapy (Hemeg, 2017; Ibraheem *et al.,* 2019), cancer therapy (Çeşmeli and Biray Avci, 2019), stem cell therapy (Vissers *et al.,* 2019) and more. Many FDA approved nano-drugs are already being traded in the market including Ontak®, Zanaflex®, Emend®, Rebinyn®, Marqibo®, Doxil®, etc. and more are under clinical trials (Ventola, 2017). Even though the nanotechnology approach for treating infectious diseases and medical conditions is promising, still there are some limitations/challenges that need to be addressed.

The major gap is the lack of extensive research related to in vivo effects and pharmacodynamics and pharmacokinetics of nanoparticles. A lot of research has been done in in-vitro and animal models but little or no research has been done to observe their effects on the human body (Wim *et al.,* 2008; Zhao and Jiang, 2013). This is mainly due to strict regulations of FDA and also animal models are not capable of completely depicting human models. To put it simply, we lack the necessary understanding of biological patterns of nanoparticles at both cellular and organ level (Wim *et al.,* 2008).

One of the gravest challenges of employing nanodrugs in clinical markets is the cost-effectiveness. The product Nutropin Depot® is a Poly Lactic-co-Glycolic Acid (PLGA) loaded with Human Growth Hormone. Its production was later decommissioned due to cost-effectiveness (Stevanovic and Uskokovic, 2009).

Moreover, toxicity remains one of the major limitations in the clinical use of nanomaterials. The composition of nanoparticles along with their physiochemical properties such as shape, size, charge, etc. play a crucial role in their toxicological properties (Sharifi *et al.,* 2012). There is a substantial lack in the understanding of the interaction of cells and tissues with nanomaterials in a live environment. Some studies suggested that interaction between cells and nanomaterials causes the generation of free radicals. These free radicals give rise to intracellular oxidative stress, which may result in pulmonary toxicity and hepatotoxicity (Wim *et al.,* 2008). Kim et al. (2009) observed that Ag+ and Ag NP both induced cytotoxic effects on human cells by using different mechanisms, when used in higher concentrations. Nanomaterials can cause damage to our microbiome, increase heart rate, induce oxidative lesions, cause cellular abnormalities, abnormal sedimentation, and hem agglutination. Nanoparticles are also thought to be associated with Chromosome segregation, obstruction of cytokinesis, and centrosome duplication. The charge on the nanoparticle's surface also affects their toxicity (Khan *et al.,* 2016; Naskar and Kim, 2019; Zhang *et al.,* 2010).

The toxicity of nanoparticles can be reduced or eliminated by using various strategies. One of the most effective techniques is the capping of nanoparticles by using a biocompatible biopolymer such as chitosan or polyethylene glycol. This not only tends to lower the toxicity of the NPs but also helps in enhancing the biocompatibility (Naskar *et al.,* 2016) (Cinteza *et al.,* 2018). Doping is another effective strategy used to lower toxicity of nanoparticles. Reports showed that Fe-doped ZnO, Zn-Ag-doped hydroxyapatite, Ag NPs doped on a graphene film, and ZnO-doped TiO_2 nanocrystals not only showed lower the toxicity levels but also enhanced biocompatibility (Naskar and Kim, 2019).

The small size of nanoparticles contributes to their larger surface area but can result in particle-particle aggregation, which hampers the physical handling of the particles. Limited loading of drug and burst release also contributes due to the above-mentioned properties (Patel *et al.,* 2017). Higher free energies of nanoparticles are the cause of agglomeration and aggregation. This can be minimized by coating nanoparticles with specific surfactants e.g. sodium oleate or polymers e.g. dextran, chitosan, polyethylene glycol (Gupta *et al.,* 2019b). Nanosystem preparation encounters another hindrance in the form of aggregation and stability, as some hydrophilic peptides may leak from the systems; when they are encapsulated into a hydrophobic system containing an aqueous layer. Nano vehicles are used for delivering a drug to target tissues. Encapsulated peptides sometimes interact with the walls of nano-carries, affecting their release, in the nano-environment. Thus, causing the phenomena known as the incomplete release (Mohammadi-Samani and Taghipour, 2015).

Nanoparticles were employed in antimicrobial therapy to treat multiple drug resistance organisms (MDROs) but the risk of development of resistance to NPs is there. Microbial cells may develop resistance toward NPs through multiple mutations (Singh *et al.,* 2018). The increased clinical use of Ag NPs raises concerns over the development of bacterial resistance towards Ag NPs (Barros *et al.,* 2018). Alteration of the genetic material of bacteria may result in the evolution of bacterial resistance towards Ag NPs (Graves *et al.,* 2015), and horizontal transfer of genes responsible for antibiotic resistance may be promoted by Al_2O_3 NPs (Hemeg, 2017). Resistance to nanoparticles by microorganisms will always be an important clinical concern. Although rare, bacteria have shown resistance towards Ag, Au, Cu NPs even after one dose (Finley *et al.,* 2015; Zazo *et al.,* 2016; Zhao and Jiang, 2013).

The use of specific alternative combinations of NPs and antibiotics can prevent the emergence of NP resistant organisms and might even help to derive the organisms back to their drug-sensitive state but their clinical use requires a prior in-depth and overall determination of pharmacokinetics/pharmacodynamics profile.

CONCLUSION

Antibiotic resistance is one of the hot topic now days. Carelessness regarding usage of antibiotics is the major cause of antibiotic resistance. By microbial resistance questions are being raised on the efficiency of antibiotics. But still scientists are looking for alternative medication approaches. Nanoparticle mediated approach is easy and safe. Many research attempts have been done on this. Practices have been continuously in progress. Peptides based nanoparticles are proving to be successful and opening a new phase of research. However, these are not so cost effective and scientists are looking for the production of synthetic peptides too. In short, nanoscience is proven to be good approach in the medication.

ACKNOWLEDGMENT

This study doesn't have any funding source. Authors acknowledged Biswaro et al. (2018) for giving permission for the adaptation of the Figures 3 and 4.

CONFLICT OF INTEREST

The authors declare that this article's content has no conflict of interest.

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