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NANOPARTICLES TO COMBAT ANTIMICROBIAL RESISTANCE: A BEACON OF HOPE?

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ABSTRACT

Antimicrobial resistance is a major threat to both human health and the global economy. The World Health Organization has identified three highly resistant Gram-negative bacilli (GNB) spreading antimicrobial resistance worldwide through several mechanisms. Mostly the prevalent GNB of critical priority display antimicrobial resistance and are associated with serious and often fatal infections. Nanoparticles have emerged as one viable option to replace the lack of new antibiotics and are thus a strong beacon of hope for overcoming widespread drug resistance. NPs have been found to exhibit broad-spectrum antibacterial properties. Application of nanomedicine requires a clear understanding of the dynamics of nanoparticle interactions with hosts and bacteria at physical, immunological, and biological levels. In this review, the mechanisms of antimicrobial resistance (AMR) and the novel uses of nanoscale functional materials as a superior alternative to traditional antibiotics are discussed. We addressed the potential, challenges, and benefits of using nanoparticles to fight AMR.

KEYWORDS: antimicrobial resistance, gram-negative bacilli, nanoparticles, carbapenemase, oxidative stress.

INTRODUCTION

Alexander Fleming heralded the beginning of the "antibiotic revolution" followed by the discovery of several new antibiotics in the 1970s and 80s.[1] Unfortunately, the inappropriate clinical and non-clinical usage (eg, in farm animals, aquaculture, poultry, meat and plants) impacted the therapeutic efficacy leading to an exponential increase in antimicrobial-resistant bacterial strains.[2] As a consequence, pathogens evaded standard therapeutic approaches using enzymatic inactivation of antibiotics, reduced cell permeability, reduced target accessibility, target overproduction, altered target site/enzyme, increased efflux from overexpression of efflux pumps and others.[3] Other more complex mechanisms such as biofilm formation and quorum sensing also contribute to antimicrobial resistance (AMR).[4] An insight into microbial genetics would throw light on several intrinsic and extrinsic factors playing a major role in spread of AMR globally. Depending on where the resistance genes originate, resistance might be classified as either acquired or inherent. While acquired resistance results from acquiring resistance genes from another organism, intrinsic resistance can arise from spontaneous mutation of existing genes. The same bacterial cell can acquire several drug resistance genes, leading to the establishment of multidrug resistance (MDR) in particular. Three mechanisms exist for the transfer and dissemination of resistance among bacteria: integrons, transposons, and plasmids.[5]

AMR disproportionately affects vulnerable groups such as children and newborns and the elderly population, with pneumonia and bloodstream infections (BSI) being among the leading causes of higher mortality rates. AMR has evolved faster than the discovery of new antibiotics.[6] The World Health Organization (WHO) Global Antimicrobial Resistance and Surveillance System (GLASS) reports a steep increase in antibacterial resistance, leading to significant mortality and morbidity.[7,8] Gram-negative bacilli (GNB) are an emerging cause of concern due to the fact that are capable of causing both community- and hospital-acquired illnesses.[9] The WHO in 2021 published a priority list of antimicrobial resistant pathogens which require new antibiotics to be categorized as “reserve”

antibiotics in the WHO AWaRe (Access, Watch, Reserve) classification. These pathogens required new antibiotics to curtail their spread as they could easily evade drug action.[10] The WHO has subsequently identified carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant Pseudomonas aeruginosa (CRPA) and carbapenem-resistant Acinetobacter baumannii (CRA) as pathogens associated with critical or severe disease on a global priority list of pathogens.[11] The steep rise in AMR is mainly attributed to selection pressures on sensitive bacteria.

The carbapenemase enzymes produced by the carbapenem-resistant Gram-negative bacilli (CR-GNB) render carbapenem antibiotics, inactive. Carbapenemases fall into one of three categories: class A, which includes serine in the enzyme's active site (e.g., SME, IMI, NMC, GES, and KPC); class B, which includes metallo-beta-lactamases (MBLs) (e.g., IMP, NDM, VIM, and GIM); and class D (OXA-like). Mobile genetic elements (MGEs), which might be transferred across strains, contain the genes that code for several carbapenemases.[12] Further restricting treatment options for CR-GNB infections is the fact that these MGEs frequently include additional genes that confer resistance to non-lactam antibiotics.[13]

1.1 MULTIDRUG RESISTANCE AND NOVEL ANTIBIOTICS CRISIS – A BIG CHALLENGE

The new antibiotic pipeline is drying up. It is clear that a lot needs to be done to stimulate the antibiotic research and development ecosystem for sustainable and equitable antibiotic access. It is time to think about antibiotics as a "Global Public Good".[3] MDR bacteria are of serious concern in hospitals, particularly in critically ill patients.[14]

1.2 NANOMATERIAL STRUCTURE ANALOGOUS TO NATURAL BIOLOGICAL STRUCTURES

Nanoengineered materials are becoming increasingly significant in the field of medicine owing to their excellent size dependent properties, large surface to volume ratio, reactivity, and tunability, which render them appropriate for particular targeting, administration of drugs, controlled release, biocompatible films and coatings, etc. (figure 1). This facilitates high drug loading capacity and accuracy in reaching to the target cells.[6,15,16]

By altering matter at the atomic and molecular level, nanotechnology enables the development of innovative molecular forms and new technological innovations thus addressing AMR concerns. This involves creating and controlling the properties of specific materials in a nanoscale system by either scaling up a single nanoparticle quantity (bottom-up approach) or scaling down the bulk material to the desired nanometer scale (top-down approach). The size-dependent properties of nanoscales make nanomaterials powerful candidates for use in medical diagnosis, therapy and regeneration of malfunctional tissues.[17] In addition, the size of nanomaterials is analogous to natural biological structures such as proteins and DNA, which facilitates the direct integration of nanomaterials into biological systems.[18]

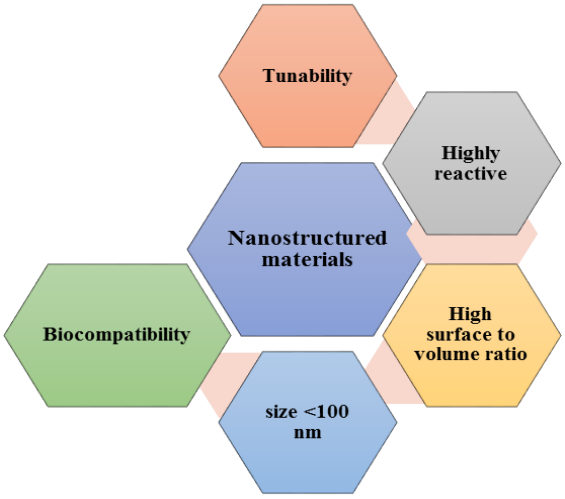

Figure 1: Properties of nanostructured materials making it suitable for nanomedicine.

2. NANOPARTICLES AS DRUG DELIVERY SYSTEMS

Since NPs are effective against both Gram-positive and -negative bacteria, they could be used towards effective therapy. NPs have been employed as carriers for the delivery of antimicrobial groups that significantly improve their biocidal activity.[6] Some benefits of using NPs as vectors are their small and controllable size, protective action against enzymes that would otherwise destroy antimicrobial compounds, ability to actively deliver antibiotics and ability to combine various therapeutic methods onto a single nanomaterial (e.g., multiple antibiotics/compounds inside the same NPs for combined action). Delivery to the target location in ideal dosage, protection against enzymatic deactivation with fewer side effects and increase their therapeutic efficacy

are some of the advantages in using NPs. Although several materials, such as liposomal and polymer-based nano-drug carriers, have been investigated, metallic vectors, such as gold NPs, are appealing as core materials due to their fundamentally inert and nontoxic nature.[4]

2.1 ANTIBACTERIAL MECHANISM OF NPs

NP carriers can fight against bacterial threats "passively," by keeping drugs at the specific infection site for an extended period of time, or "actively," by surface-coupling with active molecules that bind a specific target.[5] The balance between the drug concentration and the nanoparticle size and stability, as well as the intensity of the surface modification interactions is caused by electrostatic attraction, van der Walls forces, or hydrophobic interactions[19] (Figure 2 a,b).

When creating a successful "active" delivery strategy[20], the compound release rate and conjugate stability should be carefully taken into account. According to Wang and coworkers[5], the most frequent antibacterial mechanisms are those that involve oxidative stress, metal ion release and non - oxidative processes. However, the diverse nature of the effect of NPs makes it difficult to identify the precise mechanisms of action.[21]

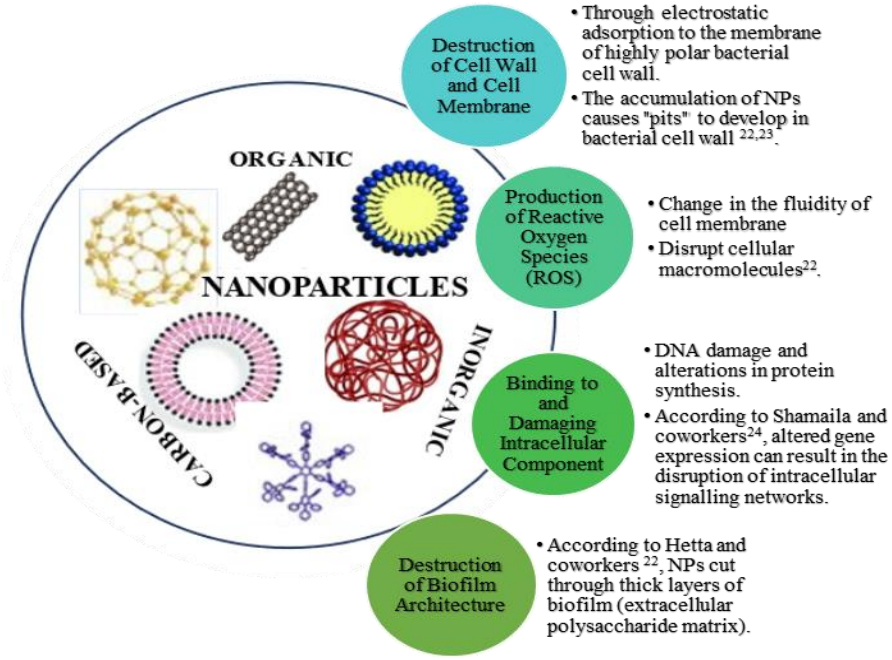

Figure 2 (a): Mechanisms of action of nanomaterials to battle Multidrug resistance.

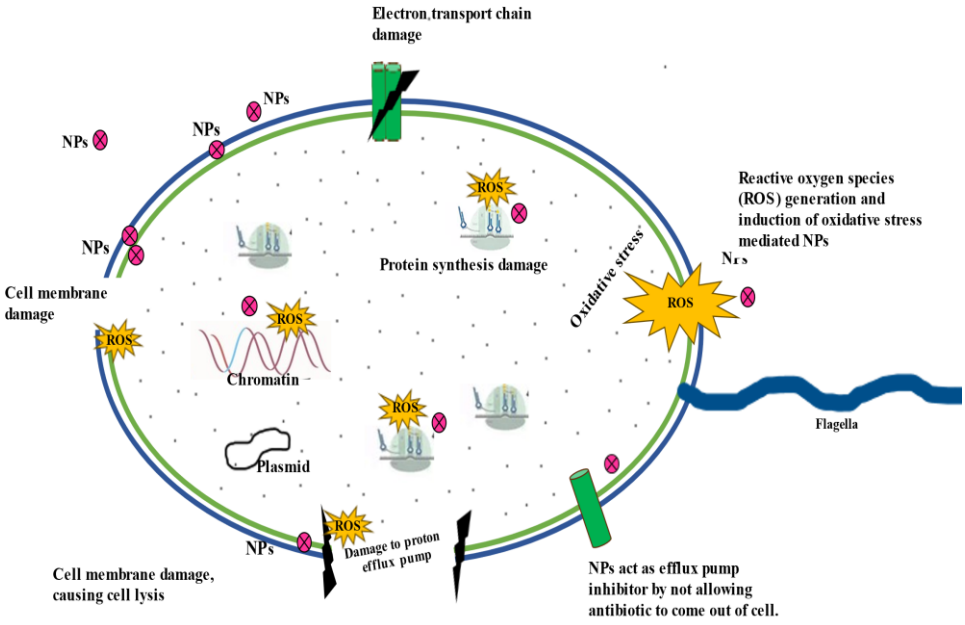

Figure 2 (b): Antibacterial mechanisms of Nanoparticles (NPs).

3. AN OVERVIEW OF NANOMATERIALS

On the basis of their molecular structure, nanomaterials may be divided into three categories: organic (liposomes and polymers), inorganic (metals, metal oxide, semiconductor, ceramic, and quantum dots) and carbon-based (Carbon nanotubes, Fullerenes) (Figure 3).

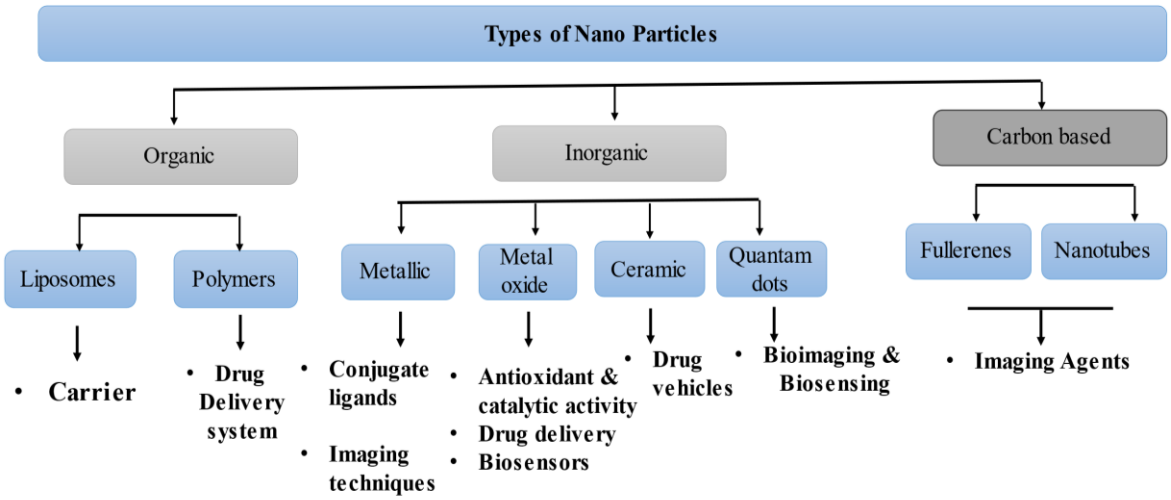

Figure 3: Types of Nanoparticles and their prospective applications.

Usually, NPs maintain the chemical characteristics of their bulk constituents, which is advantageous when selecting a particular NP for a biological application. The following NPs are utilised in nanomedicine.

3.1 Organic NPs - Liposome Nanoparticles - According to Daraee and others[25], liposomal drug delivery utilises the interaction of liposomes with cell membranes through a passive or mediated pathway to release the medication that is loaded into the cell membrane of the targeted cell. Additionally, other functional groups can be added to the liposome's exterior surface to give it more properties. This surface modification develops a layer that is highly hydrated and inhibits the development of unwanted plasma-protein coronas. Liposomal formulations have two drawbacks: instability and osmotic fragility. These drawbacks make their usage difficult since the encapsulated medications can then leak out through the bilayers.[26]

3.2 Organic NPs - Polymeric Nanoparticles - In general, the polymeric nanoparticles target bacteria's cell walls either passively or actively. Passive targeting damages the bacterial membrane and is dependent on the particle's size. In the case of active targeting, the polymeric nanoparticles are first functionalized with certain antibodies and aptamer bacteriophage proteins, which in turn are in charge of the pathogen identification and interaction with the polymeric nanoparticle. Chitosan, a polymeric nanoparticle, is frequently employed either by itself or when combined with other metallic ions, such as copper, manganese, zinc, iron, and silver, to prevent the spread of both gram-negative and gram-positive bacteria. They have the additional advantage of releasing drugs in response to stimuli to combat biofilm cells.[27]

3.3 Organic NPs - Dendritic Nanoparticles - Dendrimers are 3D morphologies with branches that are typically symmetric at their centre. They are excellent candidates for drug administration because of their distinctive spherical morphology, multivalency, and high degree of branching.[28] Dendrimers' hydrophobic characteristics can be changed by functionalizing the outer shells with groups of various groups of polarities and charges. The antibacterial effectiveness of dendrimers is determined by the attached functional group. The cationic interactions with negatively charged bacterial cells that cause the dendrimers' antibacterial activity. These ionic interactions cause the membrane protein to break down and enhance dendrimer internalisation, which disrupts the potassium ion distribution across the bacterial cell and causes it to die.[29]

3.4 Inorganic Metallic NP – Metal based nanoparticles are most widely chosen nanocarriers for antimicrobial drugs.

These metallic nanoparticles have significant antibacterial activity as demonstrated by nanoparticles of gold, silver, copper, titanium, nickel, and zinc. This activity depends on the nanoparticles' composition, intrinsic characteristics, surface functionalization, and the bacteria they target. Electrostatic interactions between positively charged metallic nanoparticles and the negatively charged bacterial cell wall cause them to be drawn to one another. The cell wall is damaged as a result of the rupture of the cell membrane by these metal-based nanoparticles. Additionally, the metal ions that are released by these metallic nanoparticles have the ability to enter cells and interfere with their normal functioning.[30] Silver nanoparticles work well as growth inhibitors for bacteria that are resistant to antibiotics.

They have the ability to inhibit bacterial growth by interacting with bacterial membrane proteins and DNA that contain complexes of phosphorus and sulphur. They work well against methicillin-resistant strains as well as gram-positive and gram-negative bacteria.[31]

3.5. Inorganic Metal Oxide NP

These NPs display antioxidant properties, catalytic abilities, along with chemical stability, optical traits and biocompatibility, all of which make them excellent for use in a variety of biomedical applications. Iron oxide (Fe3O4), titania (TiO2), zirconia (ZrO2) and more recently ceria (CeO2) are the most often used materials.[32] Due to its biocompatibility, chemical stability, and optical characteristics TiO2 is a material that is extensively explored and has valuable uses, such as being a biosensor.[31]

3.6 Inorganic NPs - Quantum Dots

Quantum dots are semiconducting inorganic metallic oxides with extremely narrow and adjustable emission bands and size-dependent features thus enhancing their usage in biological systems. However, in order to use quantum dots for biomedical applications, they must fundamentally go through several preparation and synthetic steps to assure their solubility and biocompatibility. Due to their great structural stability and photoluminescence characteristics for imaging and photodynamic treatments, quantum dots offer an advantage over traditional antibiotics. Quantum dots are functionalized or coupled with polymers to increase their antibacterial effectiveness.[33]

ZnO quantum dots are known to be effective antibacterial agents against several fungi, gram-positive and gram-negative bacterial species. The production of ROS is the basis for ZnO's destruction mechanism activity, which is then followed by the release of Zn++ ions and finally the perioxidation of lipid.[34] The cell's metabolic and reproductive functions are inhibited by the rise in oxidative stress. ZnO quantum dots' antibacterial effectiveness may be customised and enhanced by adjusting their size and concentration.[35]

3.7 CARBON-BASED NANOPARTICLES. The remarkable biocompatibility and distinctive physiochemical characteristics of carbon-based nanomaterials have attracted considerable interest. Based on their dimensions these carbon nanostructures categorized as follows.

- **Zero dimensional (Fullerenes, Carbon dots)** - Fullerene is an excellent drug delivery vehicle which is attributed to its distinctive hollow cage-like shape and structural similarities to cellular vesicles.[36] They exhibit a variety of biological behaviours as they may function as both an acceptor and a donor of electrons. Fullerene transform the molecular oxygen already present in the cell upon exposure to UV or visible light into highly reactive singlet oxygen that can rupture cellular membranes and stop numerous enzymatic processes that lead to DNA cleavage.[37]

- **One dimensional (Carbon Nano Tubes including single-walled (SWCNT) and multi-walled (MWCNT)** - Single Wall Carbon Nano Tubes (SWCNT) and Multi Wall Carbon Nano Tubes (MWCNT) are hollow, nano-dimensional cylinders made of graphene sheets. Due to their physical characteristics, including as high electrical conductivity and superior mechanical strength, CNT are thought to be useful in biomedical applications.[38]

- **Two dimensional (Graphene)** - The physiochemical characteristics of graphene nanosheets are attributed to their antibacterial behaviour. These nanocomposites enclose the bacterial cells in such a way that they slow down their metabolic processes and result in cell death.[39]

4.0 NPS EFFECTIVE AGAINST MDR PATHOGENS

Veriato and coworkers[40] states the use of Ag-NPs and vancomycin to break down the cell walls of resistant *Enterococcus faecalis* and *Staphylococcus aureus* strains.

Table 1: Nanoparticles against MDR pathogens and their mode of action.

Pathogen involved	Infection	Antibiotic resistance mechanism	NPs	Mode of action	Reference
Acinetobacter baumannii	Infections associated with medical devices and Pneumonia; mucous membrane; wound/injury.	Production of Biofilms and β-lactamases, alteration of cell components and virulence genes.	AgNP	Downregulation of virulence and biofilm-related genes by AgNPs	[22]
Pseudomonas aeruginosa	Life-threatening infections and Nosocomial bacteremia.	Production of Biofilm, increase in outer-membrane permeability, antibiotic efflux pumps, β-lactamases production, virulence factors.	AgNP	Silver ion alters bacterial membrane protein, followed by cellular oxidative damage.	[42]
Klebsiella pneumoniae	Causes infections in multiple organs	Extended-spectrum (ESBLs)/ β-lactamases	AgNP, AuNP, ZnO-NP,	By binding to the cell wall, followed	[43]

	especially in patients with pre-existing medical issues.	production, loss of outer membrane proteins, change of target, increased biofilms production, altered efflux pump, integron, and virulence genes.	CuONP, TiO_2-NP, Graphene-NP.	by intracellular oxidative damage.	
E. coli	Responsible for Intestinal & extra-intestinal infections.	ESBL production, virulence factors to evade host cellular functions.	AgNP	By binding to the cell wall, followed by intracellular oxidative damage.	[44]

5.0 BIOLOGICAL BARRIERS TO DRUG DELIVERY

There are several obstacles to drug delivery (figure 4).

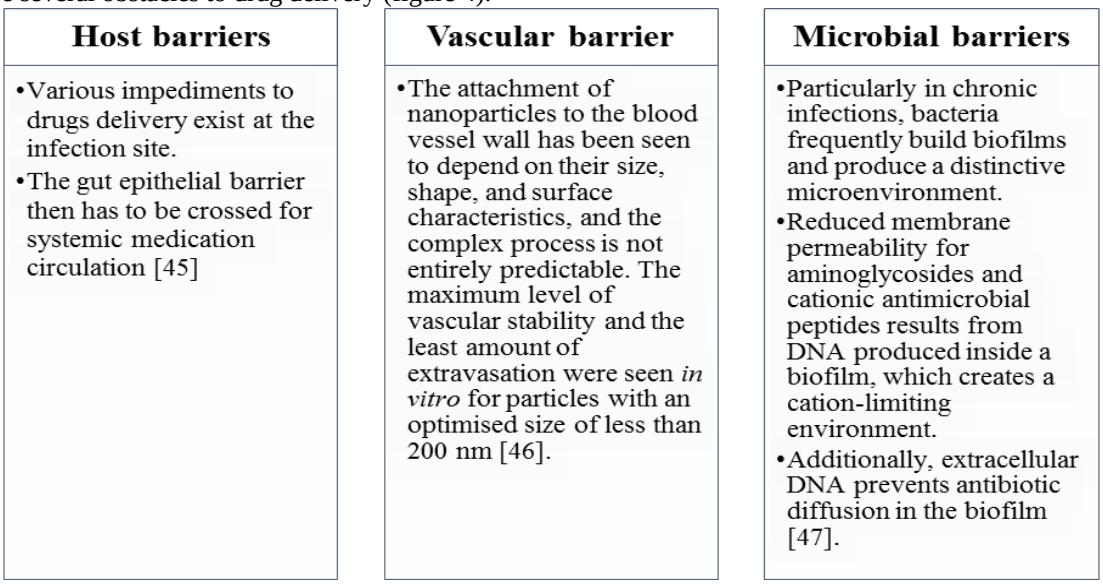

Figure 4: Barriers to drug delivery - Nanoparticles in the host need to cross various barriers to achieve targeted delivery.

Complex biological barriers are impediments to be crossed in order to achieve successful therapy. Improving drug delivery through various physicochemical barriers and increasing therapeutic indices, are certain challenges nanocarriers are designed to overcome.[47]

6.0 ANTIMICROBIAL NANO-CARRIER PAYLOADS AND DELIVERY STRATEGIES

Polymeric nanocarriers have several benefits owing to of their antibacterial action. By targeting the antibiotic localization to particular tissues and hence its biodistribution, these devices can decrease toxicity while increasing the antibiotic's potency and/or efficacy. The prospect of nanocarrier controlled release to reduce the number of administrations required might enhance compliance to treatment. Encapsulation may enhance potency and/or efficacy and lower the likelihood of resistant escape by shielding sensitive payloads from harsh chemical and biological environments during transport to the target site, such as AMPs (degradation by protease and acidic degradation), β-lactams (degradation by β-lactamase), and doxycycline (photolytic degradation). These devices have chemical functional groups that allow the targeted molecules to bioconjugate, thus guiding the nanocarriers over difficult obstacles.[48]

In order to treat vector-borne diseases, neurodegenerative disorders and cancer, drug delivery of payloads to targeted cells is achieved by accumulating nanocarrier locally into the target environment and efficiently releasing payloads without disturbing healthy cells. Such targeted drug delivery is designed using two strategies: (i) Active strategy (programming nanocarriers to target specific cells after extravasation by recognising specific membrane-based receptors on diseased cells) and (ii) Triggered release strategy (based on stimuli-responsive nanoparticles such as pH variation, redox factors, ionic strengths, temperature, magnetic fields and ultraviolet/infrared radiations, thus inducing enhanced release of payloads at diseased site).[49]

Antimicrobial Peptides (AMP) are small, cationic eukaryotic peptides containing a high proportion of hydrophobic moieties. They have a broad spectrum by acting on targets like the cell membrane and DNA. In fact, AMPs have the ability to incite the innate immune response and combat with a broad range of microbes,

including bacteria, virus, parasite and fungi. Moreover, research indicates that, these small cationic peptides have the ability to target cancer cells and can be used as therapeutic agents. Recently, AMPs have been proposed as a supplement to conventional antibiotics. AMPs are currently limited by high cost, proteolytic degradability, and limited understanding of molecular mechanism.[50]

7.0 CONCLUSION

Nanomedicines are cutting edge antimicrobial therapeutics with greater patient compliance, increased efficacy, and circumvention of physiological barriers and antimicrobial resistance. Production scale-up, cost, storage shelf-life, and regulatory permissions are challenges of concern. Future research is expected to concentrate on developing more resilient nanoparticles from synthetic or natural biocompatible and biodegradable materials.

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