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Mini Review

Green Nano-therapeutics as an Alternative to Conventional Strategies for Combating Multi-drug Resistant Bacteria

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Abstract

The increasing threat of infection caused by multi-drug resistant bacteria is a global health concern that has become a serious medical emergence due to the rapid use of novel class antibiotics for curing infections. Nanotechnology introduces innovative strategies for addressing this challenge. This article concluded the recent development in the nanotechnology field and approaches for combating drug resistance in bacteria. It includes the development of nanomaterials that directly target the resistance mechanisms such as the production of reactive oxygen species or indirectly target the resistance by interfering with cellular metabolism. Nanotechnology may emerge as a potential remedy to cure MDR bacteria.

Introduction

Multi-drug resistance in bacterial strains is genetically conferred and transferred to other strains through acquisition of plasmid by horizontal gene transfer [1]. The drug resistance in bacteria is due to the low permeability of the outer membrane, efflux pumps, and synthesis of antibiotic degrading enzymes as well as modification of targets. The exaggerated use of antibiotics for treating the infectious diseases, use of multiple-broad spectrum drugs and scarcity of novel antimicrobial agents are the key factors for the spread of multi-drug resistance (MDR) species [2].

In spite of advance antimicrobial therapies, antibiotic resistance becomes life threatening, especially in immuno-compromised hosts [3]. Among most challenging MDR infections, approx 50% due to the methicillin-resistant Staphylococcal infections and 30% due to the Vancomycin Resistant Enterococci (VRE) have been reported [4-6]. These MDR bacteria causes nosocomial infections leads to prolonged hospitalization and can be life threatening [7]. In multi-drug resistant bacterial infections, gram-negative pathogens can cause high mortality rates and leave very few effective antimicrobial options [3]. Gram-negative bacteria contain a unique component on their outer membrane like lipopolysaccharide (LPS), several proteins and phospholipids which act as a permeability barrier for excluding the various drugs and antibiotics from entering the cell. The LPS itself is toxic and categorized as an endotoxin that induces a strong immune response when bacterial infection occurs in animals [8].

Thereby we need development of novel drugs and antimicrobial strategies for combating multi drug resistant bacteria. Nano-therapeutics may confer as key factor for overcoming the bacterial resistance as nanomaterials and have desirable physicochemical properties that can induce a new line of defense against MDR microorganisms [9]. Nanoparticles have large surface area so they can directly contact with cell membrane and efficiently penetrate

the biofilm [10]. Apart from this, nanomaterials can increase the intracellular accumulation of the drugs and effectively prevent the transporter activity [11].

Green nano-therapeutics/nano-antibiotics as an alternative technology for combating the drug resistant bacteria

Nanoparticles can be synthesized through several methods such as chemical, physical and biological approaches. Chemically synthesized nanoparticles exert non-eco-friendly by-products that are toxic to cells. So, an increasing demand for eco-friendly, non-toxic approaches for nanomaterial synthesis which excludes use of toxic chemicals as by products. Biological moieties represents high antimicrobial activity which can reduce and stabilize the metal ions to produce nanoparticles capped with antimicrobial compounds, therefore particles also can improve the antagonistic potential in cost-efficient and eco-friendly manner [12] Coupling of nanoparticles with herbal antimicrobials are one of the less toxic and more-effective strategy to combat multi-drug resistant bacteria by inhibiting efflux pumps, biofilm formation, interference of quorum sensing in bacteria. Nano-scale materials can be used as antimicrobial agents or novel drug delivery carriers [13]. Kumari et al. [14] biosynthesized silver nanoparticles of different dimensions such as spherical, rectangular, penta and hexagonal in an eco-friendly manner through biocontrol agent *Trichoderma viride*, they have also performed the shape and size dependent antimicrobial activity of nanoparticles. Authors are concluded that spherical nanoparticles of 2-5nm showed excellent synergistic antimicrobial activity with antibiotics against MDR pathogens i.e., *Shigella sonnei*, *E.coli*, *Serratia marcescens*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Similarly, Giri et al. [15] formulated a Biogenic Silver Nanoparticles (BSNP) based ointment and evaluated its activity against wound-infection caused by MDR bacteria *S. aureus*, *P. aeruginosa* and *E. coli*. They found that BSNP based ointment efficiently accelerate the wound healing activity than conventional wound healer.

Besides, nano-emulsification of essential oil can be one of the effective strategies for synthesizing potent herbal formulations against MDR bacteria. Essential oil-based nano emulsions are an emerging alternative antimicrobial compound for controlling MDR pathogens. Nano emulsion synthesized from *Thymus daenensis* essential oil showed an excellent antibacterial and anti-biofilm activity against MDR bacteria *Acinetobacter baumannii* [16]. Similarly, *Cleome viscose* essential oil nano emulsion has synthesized by Krishnamoorthy et al. [17] and showed drastic inhibition of several MDR bacteria by blocking the drug efflux mechanism of methicillin-resistant *S. aureus* (MRSA), Drug resistant (DR) *Streptococcus pyogenes*, and DR extended spectrum beta-lactamase (ESBL)-producing *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. They reported that nanoemulsion disrupts the functional group of lipids, proteins and nucleic acid, leading to damage of the cell membrane and walls of drug resistant bacteria. Moreover, the bioactive phytochemicals present in the nanoemulsion inhibit the drug efflux mechanism and metabolic enzymes in MDR pathogens. Four mechanisms of antibacterial activity have been hypothesized which are as follows:

A. The accumulation of nanomaterial in the bacterial membrane affects the permeability which leads to release of intracellular biomolecules and also disrupts the proton motive force of the plasma membrane.

B. Nanoparticles produce reactive oxygen species (ROS) in the cell which leads to oxidative damage of cellular structures.

C. Absorption of nanomaterials by the cells, leading to subsequent reduction of intracellular ATP production and it also leads to DNA damage of MDR bacteria.

D. Binding of nanoparticles and its active ions with different enzymes causing arrest of cellular respiration.

The generation of reactive oxygen species, inactivation of cellular enzymes, disruption of cellular membrane, and DNA damage are some mechanisms of nanomaterials which leads to cell lysis and death of MDR bacteria [18-22].

Conclusion

The widely spread threat of multi-drug resistance create immense pressure on pharmaceutical sector to search for novel antimicrobial agents. In a battle against MDR bacteria, nanotechnology has a potential to change the conditions and prevent the spread of drug resistance. Importantly, green metallic nanoparticles as well as essential oil nano emulsions are ecofriendly, cost-effective, and known to be efficient antimicrobial agents against MDR bacteria. The article showcased the emergence of multi-drug resistance in bacteria and role of nano-therapeutics against MDR bacteria. Further work is still required in order to elucidate the whole mechanism to action of nanomaterials and toxicity of nanomaterials in humans.

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