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Role of Potential Nanomateriales in Reducing Bacterial Resistance against Antibiotics (A Review).

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Abstract :

Antibiotic resistance is one of the most serious public health issues of our generation. at least two million people get an antibiotic-resistant infection each year and 35,000 die from it each year. attacking this threat calls for a multi-sector approach. In this time, the World Health Organization (WHO) released a list of 12 families of super pathogens that are a great danger to human health, which recommended that new strategies should be developed to combat them. To date, a few new antibiotics have been discovered. A large part of this slowdown can be due to increased resistance in bacteria. The health crisis surrounding global antibiotic resistance necessitates searching for alternative solutions. Innovative and effective treatment approaches in the medical science have found their way into the realm of nanotechnology. different inorganic nanomaterials, including gold, silver, and some That makes interesting use of gold nanoparticles, as they are biocompatible, have no side effects, and offer great optical properties implementation of new antibacterial systems will concentrate on the latest studies in the area of antimicrobial gold nanoparticles.

Key words : Nanomateriales , Antibiotic resistance , Gold Nano .

Introduction :

Antibiotic resistance, one of the greatest challenges to human health in the 21st century, is the ability of bacterial cells to tolerate one or more forms of antibiotics [1] , [2]. Infections such as pneumonia and tuberculosis are becoming more difficult to manage as available antibiotics become less effective as bacterial resistance increases[3]. It's become even worse because of the reduced production of new antibiotics, alongside their excessive and abusive use[4]. This results in more patients

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spending longer in the hospital, costlier healthcare, and an increase in mortality[5]. The threat of antibiotic resistance stems from the fact that it has resulted in tremendous human and economic casualties[6]. Every year, approximately 700,000 people die as a result of excessive antibiotic use, which leads to resistance to traditional therapy. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) was confirmed to cause nearly health problems [3]. Carbapenemase has been regarded as a dangerous to peoples health, requiring timely and intrusive measures [2] . To understand how nanosystems can be used as antibacterial delivery agents, it is necessary to understand how bacteria shape colonies that resist conventional antibiotic therapy[7]. Biofilm is a developed mechanism that allows bacteria to live in stable colonies, which can dissocate and form new colonies in hostile environments [8].

The majority of bacteria are still vulnerable to antimicrobial agents, but a select few has a resistance to such antibiotics[4]. Enterococci, Staphylococci, Klebsiella, and Acinetobacter bacteria are known as "the ESKAPE pathogens." They are the principal pathogens for nosocomial infections and second, they are a model of pathogenesis and tolerance. regulation of these microorganisms may be extended to other species that try to usurp their territory [9].

This material allows numerous molecules to interact with both the host and pathogen at the nanometer level. due to this property, new medicines have emerged, which are called ‘nano-objects'. Nanostructured bulk materials are now used to inhibit bacterial attachment or to get rid of it. Nanoparticles can help reduce antibiotic use for various types of infections. on all macromolecular mechanisms (Figure1).

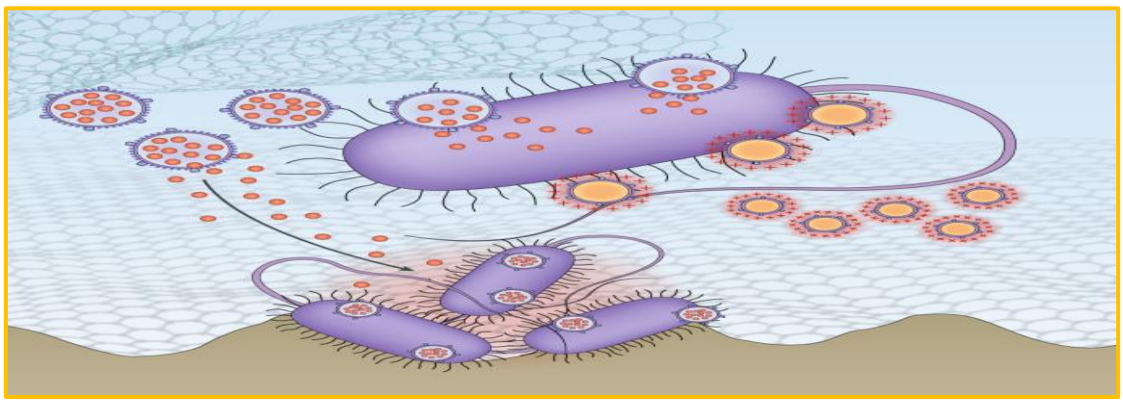

Figure 1: Nanomaterials have major potential for treating antibiotic-resistant bacterial infections.

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In this study, nanosystems will discuss the function of bacterial resistance to overcome and the various mechanisms used by nanosystems will be described as agents for antibacterial medication. Also addressed are clinical trials and problems of nanomedicine clinical translation.

Emergence of Bacterial Resistance to Antibiotics and its Mechanism of Action

Infectious diseases were the leading cause of death worldwide in the first half of the twentieth century and have risen to become the second leading cause of death in recent decades[10]. Medicine was in the dark ages for centuries, dependent on plants, fungi, and lichen to cure diseases, before research into microbial secondary metabolites contributed to the antibiotic period. Antibiotics are one of the most significant pharmaceutical discoveries, and they have been dubbed "miracle" drugs since their introduction into the health-care system in the 1940s. The discovery of antibiotics forever changed the medical industry, forever changing how medicine is practiced [11]. Antibiotics are categorised into three main groups according to the mechanism through which this action occurs table 1 [12].

Table 1 : The general classiification of antibiotics and their actions.

Antibiotic class	**Target**	**Example(s)**
β-Lactams	Peptidoglycan biosynthesis	Penicillins (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)
Aminoglycosides	Translation	Gentamicin, streptomycin, spectinomycin
Glycopeptides	Peptidoglycan	Vancomycin, teicoplanin
Tetracyclines	Translation	Minocycline, tigecycline
Macrolides	Translation	Erythromycin, azithromycin
Lincosamides	Translation	Clindamycin

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Streptogramins	Translation	Synercid
Oxazolidinones	Translation	Linezolid
Phenicols	Translation	Chloramphenicol
Fluoroquinolone	DNA replication	Ciprofloxacin
Pyrimidines	C1 metabolism	Trimethoprim
Lipopeptides	Cell membrane	Daptomycin
Cationic peptides	Cell membrane	Colistin

Bacterial resistance started in the 1950s, when penicillin resistance was of particular concern It was quickly remedied with the use of beta-lactam antibiotics, but in 1961 the first case of methicillin-resistant Staphylococcus A began appearing in the UK as well. At the end of the 1960s through the 1980s, however, antibiotic resistance affected the likelihood of further advancements. This reduced the supply of new antibiotics, and fewer were made available. Overuse, inadequate use, and excess use of antibiotics has caused the so- "antibiotic resistance" or "antibiotic abuse" in agriculture problem [13].

Bacteria can acquire antibiotic resistance through three distinct mechanisms, as illustrated in Figure 2:

(i) Antibiotics with less permeable to bacteria than those who have no antibiotics Most Gram-negative bacteria are impermeable to many antibiotics due to their outer membrane properties. Aminoglycosporizing porins either decreases or changes the available amount of antibiotic concentrations for bacteria [14] .

(ii) Antibiotic targets may be mutated, post-translational modified, or defended against. The mutation of the target part renders antibiotic molecules ineffective at binding, allowing the bacteria to survive normally and thereby developing resistance to the drug. On the other hand, even in the absence of mutations in the encoding genes, the target structure can be protected or altered, contributing to antibiotic resistance [15] .

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(iii) Antibiotic resistance is primarily caused by direct action on the antibiotics, either by hydrolysis or the transfer of a chemical group. A classic example is the penicillinase enzyme, which degrades penicillin antibiotics. Bacteria can also alter antibiotics by adding chemical groups to the active sites (acyl, phosphate, nucleotidyl, and ribitoyl, for example) to prevent antibiotics from binding to the target due to steric hindrance[16].

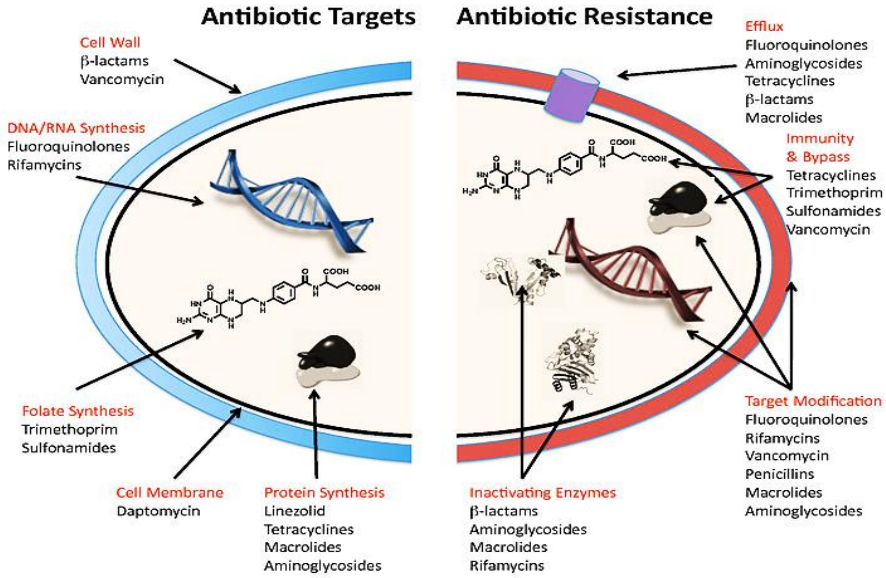

Figure 2. Mechanisms of bacterial resistance to antibiotics [17].

A variety of novel approaches to combating bacterial resistance are currently being researched, with some also making it to clinical trials. Anti-virulence strategies include toxins, adhesins, quorum sensing (QS) molecules, siderophores, and immune evasion factors, all of which are targeted to inhibit the development or action of virulence factors (VFs). Microbiome-modifying treatment, which involves manipulating and designing the human microbiome in order to avoid and resolve infection, is another appealing technique. This approach has sparked a lot of interest in academia and industry[18]. Bacteriophages, also known as phages, have gained popularity in response to the emergence of multidrug-resistant pathogens in the last 10–15 years. Phage therapy's specificity to a single bacterial species, and typically a subset of strains within that species, is one of its distinguishing features. Gold and other noble nanoparticles have also been noted for their anti-biofilm efficacy [18]. Immunotherapy, antisense RNA, drug-resistance control, and other strategies have all been extensively explored in a recent study by Theuretzbacher U *et al* (2019) [19].

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Antibiotic Resistance and Nanosystems:

Drug-resistant bacteria have developed with amentreated the restricted availability of new antibiotics, making existing approaches less effective on patients' wellbeing. Due to the difficulty in producing effect and safe new drugs, and the significant time it required for new drug approval, the new antibacterial agents were regarded as an unattractive avenue for drug development. Many antibiotics were approved for use in the United States in 2016 for clinical trials more depressing but true: Unfortunately, Teixobactin was the only approved antibiotic during the last decades, so no one could have discovered it [20].

On the basis of the above evidence, the current studies are designed to identify new strategies to meet these relevant challenges and to increase the efficacy of traditional antibacterial drugs. Nano-medicine plays an important role in improving the efficacy of existing therapies, improving the physical and chemical properties of antibiotics, giving the chance to internally integrate bio-films, extending the release of antibiotics, as well as the capability of a targeted supply to the infection site, and improving the systemic circulation with the related reduction [21].

Antibacterial Drug Delivery Agents Using Nanosystems :

The physical and chemical characteristics of nanosystems are key factors that govern critical processes like intracells, biodistribution or clearance, such as the size, the surface charging, and solubility. Size of nanometer particles improves the effectiveness of hydrophilic as well as lipophilic antibiotics, thereby improving the antibacterial impact. The reticulum-endothel system was passed along with a more planned cell internalization of the antibiotics to loaded nanosystems. Surface charging and nanosystem zeta potential interact with proteins, tissue or with different tissue elements, thereby impacting and absorbing cells. In contrast to non-charged or negative nanosystems, host cells such as anionic macrophages attract positively charged nanosystems [22].

As conventional drugs and antimicrobial agents struggle to kill resistant bacteria and biofilms in certain cases, the global quest for new tools is intensifying and becoming a necessity. Several studies show that different forms of nanomaterials (both organic and inorganic) have shown promising antibacterial activity. It has also been asserted

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that using nanoparticles is one of the most promising methods for combating microbial drug resistance.

Small particles in the range 1-100 nm in diameter are nanomaterials. At a small scale these materials have essentially different physicochemical and biological characteristics from their bulk shape. Nanomaterials are potentials for medical imaging, drug delivery and disease diagnostics because of their high surface and small-size effects. The size of nanomaterials provides a broad surface-to-volume ratio, which enables a wide range of high affinity ligands to be linked, which equip nanoparticles with a diversity in bacterial cell eradication. Nanomaterials exercise their antibacterial properties through a number of pathways.

These are, as illustrated in Figure 3:

(i) Direct contact with the bacterial cell wall;

(ii) Inhibiting biofilm formation;

(iii) Triggering of both innate and acquired host immune responses;

(iv) Production of reactive oxygen species (ROS); and

(v) Nitiation of intracellular effects (e.g., interactions with DNA and/or proteins). As nanomaterials do not possess the same mechanisms of action as regular antibiotics they can be of extreme use against multidrug resistant (MDR) bacteria [23].

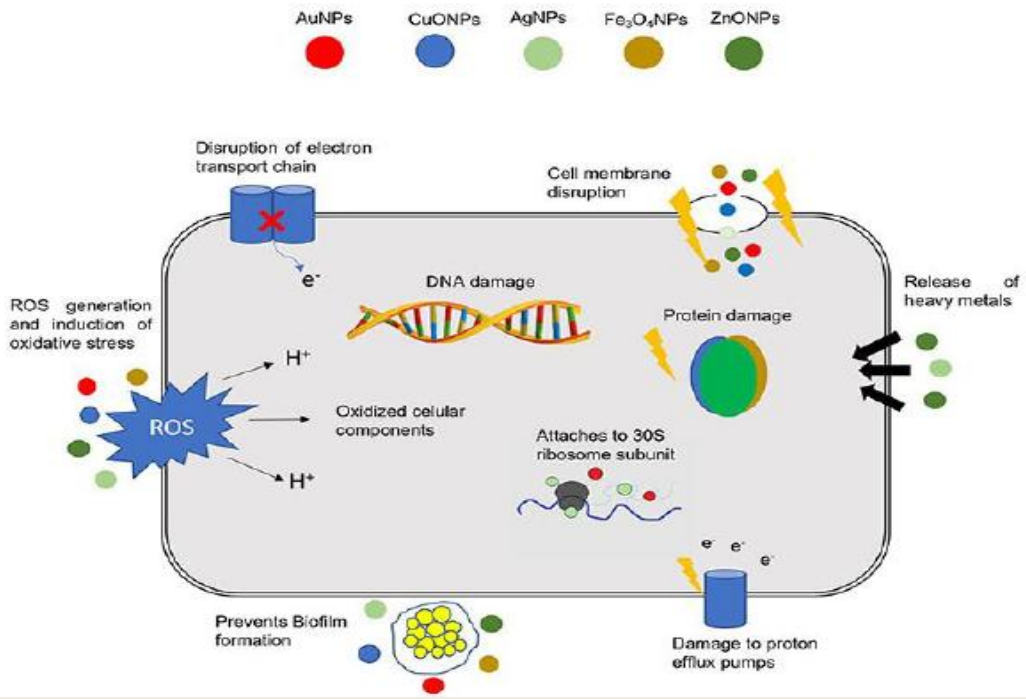

Figure 3. Different mechanisms of action of nanoparticles (NPs) in bacterial cells.[23]

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Nanosystems Classification:

Nanosystems can be classified into inorganic and organic nanosystems according to : their matrix properties and the material constituting .(Figure 4).

1- **Inorganic nanosystems** are nanosystems that are completely made up of inorganic oxides. The chemical reduction of metallic salts in the presence of a reductant is used to make them. The specificities of these materials are influenced by temperature and pH parameters in the reaction environment, which influence their loading efficiency [24].

2- **Organic nanosystems.**, like liposomes, have excellent biodegradability and bioc properties, making them safe for clinical use.[24].

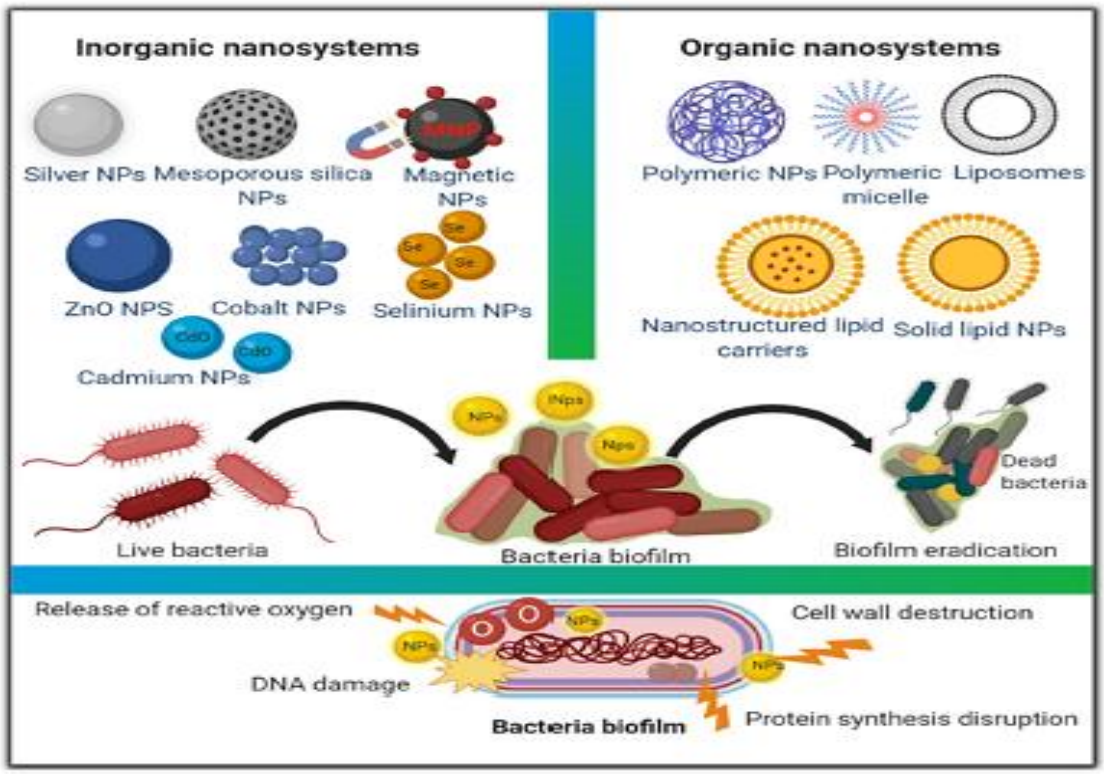

Figure 4. A graphical representation of different nanosystem groups, along with an example of their potential anti-biofilm mechanisms.[24].

Gold Nano:

Gold is known to be inert and non-toxic as a metal, although this can change as it transitions from metallic bulk to oxidation states. According to a recent analysis of the literature, gold nanoparticles of various dimensions and shapes are the most extensively studied nanomaterials for photothermal antibacterial and anti-biofilm applications. Gold nanoparticles are now being used in a wide variety of biomedical applications, including bioimaging, gene delivery, contrast enhancement in X-ray

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computed tomography, targeted drug delivery, diagnostics, plasmonic biosensing, colorimetric sensing, tissue engineering, photo-induced therapy, and cancer therapy. Chemical colloidal synthesis is a process that is often used to synthesize AuNPs. It consists of a metal precursor, a reducing agent, and a stabilizer. Alternatively, biological ("green") synthesis methods are used to synthesize AuNPs, in which microorganisms, plant extracts, or intracellular or extracellular extracts of fungi or bacteria are used [25]. Over the last decade, gold nanoparticles with a variety of different morphologies, including spheres, rods, stars, and nanocapsules, have been easily synthesized using a bottom-up method by changing the components and concentrations. Gold is a multivalent metal that can bind a wide variety of ligands, and AuNPs have been shown to be antibacterial against both Gram-positive and Gram-negative bacteria. Nanoparticles' (NPs) antibacterial mechanism of action is size dependent. Smaller NPs exert their effect by creating large irreversible pores as they traverse the bacterial cell membrane [26]. While larger NPs with a diameter of 80–100 nm are unable to freely translocate across the bacterial cell membrane, several studies have demonstrated their ability to remove bacteria. The precise mechanism of action of larger NPs against bacteria remained a mystery until a recent study established what is known as the mechano-bactericidal mechanism of non translocating NPs. Their work established that the adsorption of NPs increases the membrane tension of bacterial cells, resulting in mechanical deformation of the membrane and eventually cell breakup and death. Gold nanoparticles have gained growing attention due to their optical and electrical properties[27]. One distinguishing characteristic is their localized surface plasmon resonance (LSPR), which is critical in a wide variety of nanotechnology applications. This effect arises as the electrons on the surface of noble metal nanoparticles interact with electromagnetic radiation, resulting in LSPR. As a result, metal nanoparticles exhibit high extinction and scattering spectra, which are advantageous in a variety of applications. Antibacterial photothermal therapy (APTT) and antibacterial photodynamic therapy are the two primary approaches that use light activation to enhance the antibacterial activity of gold nanoparticles (APDT). The special and important feature of both of these methods is their difficulty in inducing bacterial resistance. In APTT, gold nanoparticles convert light to thermal energy when exposed to the proper radiation. Under this method, gold nanorods (GNRs) and nanostars (GNSs) are used to disinfect biofilms using laser irradiation, generating localized hyperthermia to eliminate

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bacteria. On the other hand, APDT is based on irradiating photosensitizers, which produce reactive oxygen species (ROS) and thus eliminate bacteria. APDT is less effective against Gram-negative bacteria than it is against Gram-positive bacteria, and combining APDT with other antibacterial agents is the most effective way to increase its effectiveness. In our study, we classified antibacterial gold nanoparticles into three broad categories, as illustrated in Figure 5 [28].

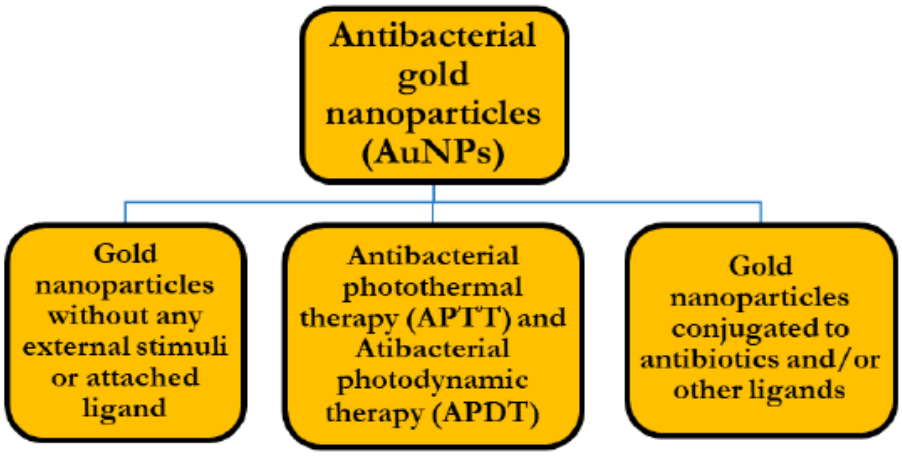

Figure 5. Classification of approaches used in antibacterial gold nanoparticles. [28]

Silver Nano-Ps :

It has been shown that Nano-Silver has significant antibacterial effects on pathogenic bacteria. Silver Nano-Ps play important role against against bacteria by interaction with the bacterial membrane and leading to cellular leakage and inhibition of cell growth . Their contact with the bacterial membrane causes bacterial cell disintegration and death, in addition to their ability to bind macromolecules. Several studies have shown that silver nanoparticles have antibacterial properties. Silver nanoparticles derived from *Corchorus capsularis* leaf extract were screened for antimicrobial activity against staphylococci, *P. aeruginosa* and *S. aureus*[29] . Furthermore, increasing the period of bacterial exposure to Ag NPs resulted in a decrease in bacterial cell survival. For the preparation of silver nanoparticles, a *Trichodesmium erythraeum* extract was used. Swaroop and his colleagues . also published a gamma irradiation-based synthesis technique for Ag-NPs[30] . Silver nanoparticles were also biosynthesised using *E. coli* culture supernatant. The manufactured particles were 33.6 nm in size on average and had a distinct shape. These results were followed by

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lower polysaccharide, lipid, protein, and nucleic acid concentrations in biofilms as compared to controls. Cationic peptides conjugated to the surface of gold or silver nanoparticles were tested for antimicrobial activity. Silver nanoparticles with cationic peptides on their surfaces outperformed gold nanoparticles with peptides on their surfaces . Owing to the high costs, silver and gold-based nanoparticles can only be used on a large scale [31].

Nano-Antibiotic

Nano-antibiotics, is a promising technique that can be used as a carrier-free drug delivery method. this approach has a lot of potential as it can impact on the physical properties of the drugs, increases their breakdown rate, reduces side effects, and enhances the ability to communicate with microbes, and makes it more efficient, and ultimately, better [30]. Morakul his colleagues looked into the efficacy of clarithromycin nanocrystals in the treatment of *Helicobacter pylori* infections. Hyperbeaded polyesters have recently been studied as a new types of nano-scale antibiotics [32] .

Silica Nanoparticles

It has been demonstrated that mesoporous silica nanoparticles can meet a variety of infection control needs, including targeting biofilms, allowing for early release, and increasing adjuvant capacity. The lectin concanavalin A-containing nanoparticles within mesoporous silica is used to treat bone infections. The treatment of bare silica nanoparticles had no effect on biofilm. The biofilm reduction was more pronounced after the addition of levoxine-loaded silica. Jang with his team examined and reported the use of seeded polymerization in order to establish the central silica–poly as a biocidal polymeric agent. Jang also explored the biocidal ability of surface-coated silica-nanoparticles. The developed mixtures (ADMH–MMA) have been utilized for the decoration of silica nanoparticle surfaces to produce a cyclic N-halamine, as antimicrobial agent, because of the hydrophobic characteristics. The silicone nanoparticles decorated with N-halamine had excellent antibacterial activity against GNB and GPB and were substantially better than their bulk counterparts' antibacterial action [33].

Zinc Oxide (ZnO) Nanoparticles

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ZnO has been licensed as a safe substance by the US Food and Drug Administration. Many recent studies have focused on ZnO as an antibacterial agent [159]. Zinc oxide nanoparticles were tested for antibacterial activity against a variety of human pathogens. The ability of ZnO-NPs to destroy cell membrane integrity, decrease hydrophobicity of the cell surface, and down-regulate certain genes in bacteria is how they work as antibacterial. Furthermore, by generating reactive oxygen species, ZnO-NPs treatment increased intracellular bacterial damage. Furthermore, ZnO-NPs avoid biofilm formation and hemolysis caused by *S. aureus* hemolysin toxin. It's worth noting that the scale of these metal oxide nanoparticles has a big impact on their antibacterial activity. Since small particles can easily pass through the pores on the bacterial cell surface, size is a significant factor. The pores on the surface of the bacterial cell are nanometer-sized. In addition, when compared to normal cells, ZnO nanoparticles showed anticancer activity. Based on the development of reactive oxygen species (ROS), the toxicity of ZnO, and the induction of apoptosis, two mechanisms were proposed. [161].

Cadmium Nanoparticles (CdO-Nps) :

Because of ion composition of cadmium nanoparticles (CDO-Nps), stability, bio-compatibility, and monodispersibility, these properties make them ideal candidates for the supply of antibacterial drugs. In order to produce the highly biocompatible, mono-dispersed and stable CDO-Nps, Zahera and colleagues employed a sol-gel method, comparing it to naked CdO-Nps. Similarly, glucose-capped CdO-Nps and naked CdO-Nps were lowest inhibitory levels against S. uraeus bacteria, respectively, at 6.42 and 16.29 mg / mL and 7.5 mg/mL and 11.6 mg / mL. In addition to improved biocompatibility and penetrability of the living cells, glucosis capping provided stability and monodispersion to CdO Nps. While nanosystems have enormous potential as antibacterial delivery agents, different bacterial strains exhibit different levels of nanosystems susceptibility. Different formulation variables should be optimized for the desired performance, such as manufacturing process, particulate size and nanosystem composition [34].

Nanomedicine's Clinical Translation Challenges :

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Clinical nanomedicine translation has challenges, such as time consumption and costly treatment. Biological problems, protection, biocompatibility, intellectual propriety (IP), legislation and regulations and overall cost-effectiveness in comparison with conventional therapies are key challenges in the field of clinical translation (Figure 6). These obstacles restrict, regardless of their efficacy, the use of nanoparticles in current markets. During clinical translation of nanomedicine, several problems should be considered. The first of them is the following nanopharmaceutical design; physical and chemical stability, biodegradability, advanced formulation design and administration. Efforts should be used to address barriers to large scale manufacturing, such as reproductivity and high cost as well as obstacles to quality control assessments of characterisation such as poly-dispersion, complexity in scalability, inadequate contaminant purification, consistency and end product storage stability, morphology, and load. Techniques to prepare large scalable amounts of nanoparticles with high levels are constantly necessary[36].

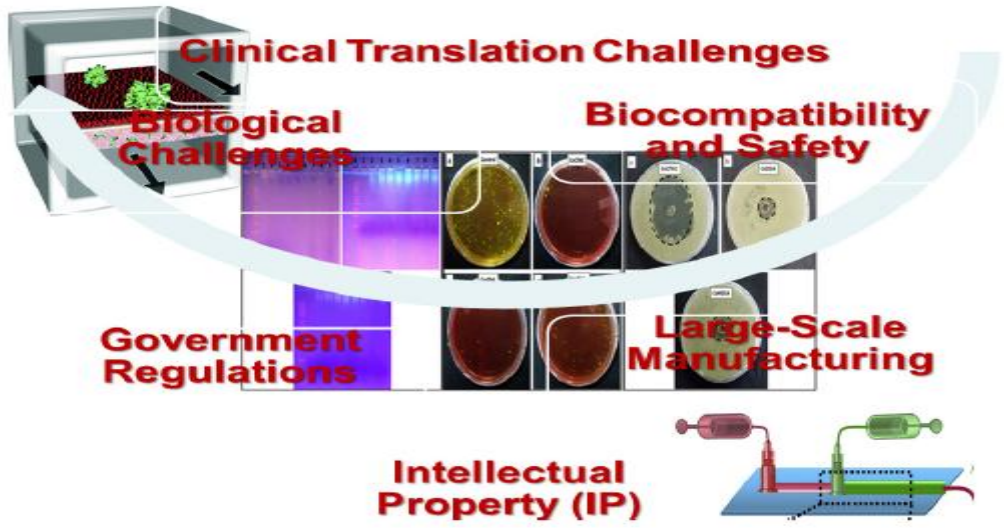

Figure 6. Graphic representation of the difficulties in nanomedicine clinical translation [37]

Conclusion :

Bacterial resistance is a very expensive and time-consuming, because of the high cost of effective new drugs to combat, effective control measures were a necessity. Nanostructured methods have recently proven effective in surmounting antibiotic resistance . The free nanosynergy or their comb in conjunction with antibiotics has been confirmed to have antibacterial properties An atomically sized system's solubility and electrical properties, for example, are critical in its use as an antibacterial agent. nanosup to alleviate bacterial resistance were detailed, along with

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the use of antimicrobial drugs with oic amphipathic and lipophilic medication, inhibiting their enzymatic activation

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