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ANTIBACTERIAL POTENTIAL OF BIO-SYNTHESIZED GOLD NANOPARTICLES AGAINST MDR BACTERIA

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ABSTRACT

The treatment of bacterial and viral infections with antibiotics is a route which is rapidly becoming more and more difficult to achieve. The start of the twentieth century was infectious disease as the leading cause for mortality worldwide. These diseases were treatable, for a time, with antibiotic development and the research coming to the fore in medical focus at this time. However, As the usage of antibiotics expanded and they were incorporated into other areas of human work, bacterium strains resistant to antibiotics started to appear. The genes that code for antibiotic resistance are not readily lost once they have developed in a bacterial population, in addition to the ongoing growth of resistance. These genes join the bacterial genome and become a stable part of it after integration. Treatment that can successfully address this multi-drug resistant condition gets more difficult to provide as new resistance mechanisms emerge. Antibiotic resistance can occur through a many of ways, such as the release of large amounts of antibiotics into the environment during waste water treatment, pharmaceutical manufacturing, and the presence of antibacterial agents in soaps and other products. Exposure to air exhaled from animal housing or discharged during animal transportation; ingesting contaminated water; and coming into contact with diseased farm workers or meat processors. These scenarios raise an important issue; that there is a great need for an enhancement of existing technology and techniques in the field of drug development, as well as the pressing requirement for development of new and innovative treatment methods for infectious diseases. A long-term material to these resistance problems that can and will be used as a foundation for further medical research in these fields has to be the goal of the research priorities. The answer to this problem may lie in the relatively discovery of antimicrobial nanomaterials, technology against which the pathogens cannot able to develop a resistance mechanism. The nanomaterials themselves would act as precisely engineered plat forms from which drugs may be delivered to target physiological sites.

INTRODUCTION

The World Health Organisation (WHO) declared in 2017 which 12 families of bacteria are multidrug resistant (MDR) and which are the greatest threats to human health. The WHO also suggested that additional steps be taken to encourage the development of modern treatments against these superbugs. In the past 20 years, not many antibiotics have been created. The increase in bacterial resistance, which is discouraging pharmaceutical companies from investing in novel antibiotic molecules, is partly to blame for this glacial development. Alternative approaches to addressing this worldwide issue are desperately needed, as there are few alternatives for antibiotics and bacterial resistance is growing. Medical nanotechnology has become a cutting-edge and potent treatment modality for some of the most complex medical problems. Gold, silver, and other inorganic nanomaterials have demonstrated possible antibacterial efficacies. As per Okkeh et al., (2021), gold nanoparticles (AuNPs) have garnered noteworthy interest owing to their optical characteristics, simplicity of surface functionalization, and biocompatibility. Over the past 10 years, metallic nanoparticles have garnered a lot of interest as a means of preventing the spread of diseases. These nanomaterials, in various forms, have the potential to attach to the bacterial cell surface and cause membrane damage. This damage can then change the membrane potential and permeability, which can result in cytoplasmic leakage and further cellular harm. Furthermore, several forms of reactive oxygen species (ROS) as intracellular are produced by metal nanoparticles, damaging microbial membranes and other cellular components and ultimately leading to cell death. Silver and gold metal nanoparticles have already been shown to have antibacterial properties. Due to their tiny different size and high surface area to volume ratio, gold nanoparticles (AuNPs) have reportedly been employed widely in diagnostics and therapies *(Akhtar et al., 2021)*.

Antibiotic Resistance

Medicines that prevent and treat bacterial infections are antibiotics. Resistance to antibiotics results in greater medical expenses, longer stays in hospital and increased patients' mortality. The world urgently needs to alter how antibiotics are prescribed and used. Even when new treatments are discovered, antibiotic resistance remains a significant danger (WHO). Microorganisms that exhibit resistance to three or more antibiotic categories to at least one antimicrobial agent are known as multiple drug resistance (MDR), multidrug resistance, or multiresistance *(Magiorakos et al., 2012)*.

The 21st century has seen a significant increase in the threat of antimicrobial resistance to public health worldwide. If the issue of antibiotic resistance is not rapidly addressed, it is predicted that by 2050 there would be 10 million annual fatalities and up to $100 trillion in economic losses worldwide. There is mounting evidence of a significant incidence of multiresistant Gram-negative bacteria in recent years, particularly in the Enterobacteriaceae family. Drug-resistant bacteria have mostly emerged as a result of the incorrect use of antibiotics in agriculture, veterinary care, and human health. According to Dougnon et al., (2021) Food items and the surrounding environment can spread gram-negative bacteria. Antibiotic-resistant bacteria may exist outside of hospitals as multidrug-resistant organisms have been found often in community settings in addition to the hospital environment. Therefore, in order to develop ways to prevent resistance from emerging and spreading and to create novel treatment approaches against organisms that are resistant to several drugs, it is crucial to understand the biochemical and genetic foundation of resistance *(Hoffman 2016)*.

Antibiotics have revolutionised medicine and saved millions of lives, but their effectiveness is under jeopardy due to the fast-global spread of resistant bacteria. Many decades after antibiotics were initially used to treat patients, the threat posed by bacterial infections has returned. The overuse and abuse of antibiotics, together with the pharmaceutical industry's inability to create new drugs as a result of difficult regulatory requirements and diminished financial incentives, have been linked to the antibiotic resistance issue, figure (1) *(Ventola, 2015)*.

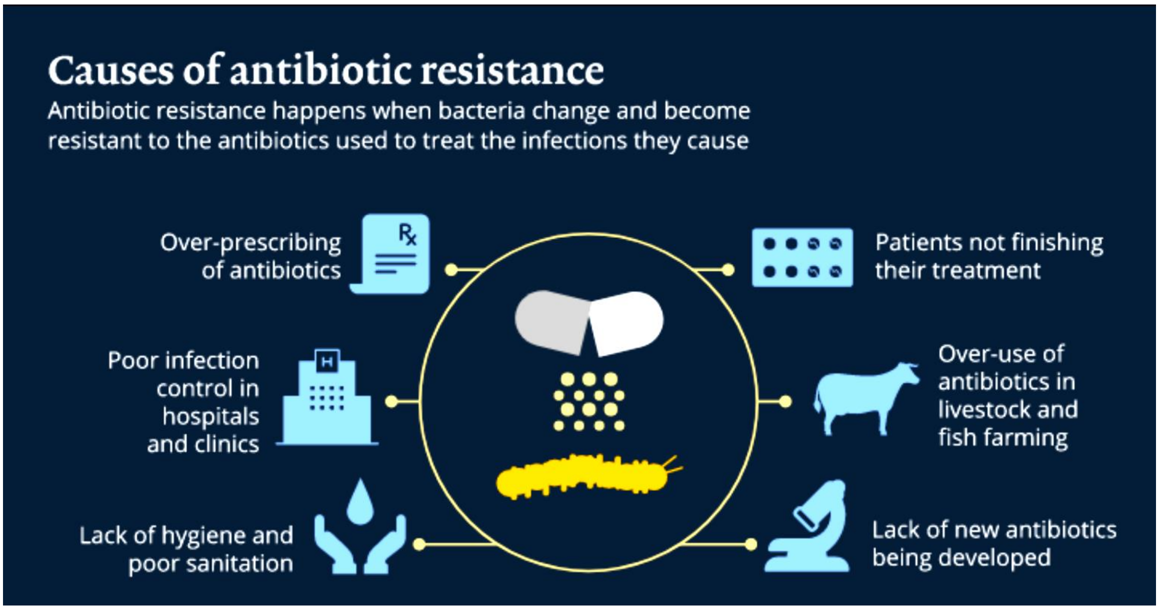

Figure 1. *(Main Causes of Antibiotic Resistance (Scientific American).)*

The Role of Nanoparticles in Development Antibiotic

Because of the decreasing effectiveness of antibiotics—which causes high infection-related mortality rates and high costs associated with health recovery—and the unfavourable outlook for the future, antimicrobial resistance is now being studied by researchers as a global health issue. Even while antibiotic resistance develops naturally, improper antibiotic usage in recent decades has led to a fast increase in both its appearance and dissemination. Transferring genes that encode antibiotic resistance makes a bacterium resistant to antibiotics. Since bacteria are continually changing, so too do their defence systems. Antimicrobial resistance is mostly a result of materials changed at the nanoscale, which enables a large number of molecules to combine to form a dynamic interface. The primary goal of the creation of these nanoparticles, which serve as carriers, is to introduce the temporal and geographical release of the antibiotic payload. They also provide new antibacterial strategies for the bacteria, which are unable to defend themselves. Therefore, by lowering total antibiotic exposure, nanoparticles serve as an auxiliary mechanism to increase medication potency. Antibiotics may be delivered to the cytoplasm of these nanostructures to suppress bacteria, even in the presence of cell barriers *(Balderrama-González et al., 2021)*.

Because gold particles are biocompatible, they are primarily and widely used in living organisms. The nanoparticles can destroy bacteria and cancer cells by photothermal heating when exposed to near-infrared radiation. For photodynamic antimicrobial chemotherapy, gold nanoparticles and photosensitizers can be coupled. By using photodynamic antimicrobial chemotherapy and near-infrared photothermal radiation, gold nanorods and photosensitizers can eradicate methicillin-resistant Staphylococcus aureus (MRSA) germs.

Using a laser, photothermally killing Staphylococcus aureus can be achieved by conjugating specific antibodies with light-absorbing gold nanoparticles. Antibiotics can be added to gold nanoparticles to increase their antibacterial activity effectiveness. When gold nanoparticles were used to cap vancomycin, the antibiotic's antibacterial efficacy against vancomycin-resistant enterococci (VRE) increased (Ali, 2016). When gold nanoparticles are utilised, the surface area accessible for microbial exposure on gold ions is greatly increased. Normally, gold is employed in the nitrate form to have an antibacterial effect. Using atomic scale material tailoring, nanotechnology is expected to provide a new avenue for the prevention and defence against disease-causing microbes. The synthesis of nanoparticles with chemical compositions, controlled morphology and varying sizes, that are suitable for mono-dispersibility is crucial in the realm of nanotechnology since these particles have special qualities that are not present in bulk materials *(Senthil Kumar et al., 2017)*.

Because of their intriguing shape- and size-dependent properties, non-toxic nature, simplicity of synthesis, and wide range of uses, gold nanoparticles, or AuNPs, have a prominent place in the field of nanotechnology. Because of their tiny size, large surface area, and unique behaviour, AuNPs provide unique benefits in nanotechnology. AuNPs can be synthesised as gold nanorods, nanospheres, nanocages, nanobelts, nanostars, and nanoprisms, among other configurations. Numerous techniques, such as chemical, physical, and biological ones, have been developed for the synthesis of gold nanoparticles. In the world of medicine, AuNPs have shaped revolutionary advancements that are being utilised in targeted medication delivery, imaging, therapy, and diagnostics *(Ali, 2016)*.

Synthesis of Nanomaterials

Because of their distinct qualities—such as their antibacterial, optical, magnetic, electrical, and catalytic activity—nanoparticles are attracting the attention of scientists due to their innovative production processes. The common methods used to create metal nanoparticles include one-phase synthesis in organic solvents, two-phase synthesis, photochemical reactions in reverse micelles, chemical, physical, biological, and mechanical procedures, electrochemical techniques, and green chemistry processes. Using chemical, physical, and biological methods, many different types of nanostructures have been synthesised, including nanocubes, nanowires, nanorods, nanoplates, Nano tadpoles, and nanobelts *(Ali, 2016)*. The discovery of antibiotics is among the most noteworthy and significant accomplishments in the medical domain. In critical care settings such as surgery, organ transplants, and the management of diverse bacterial infections, they are now considered indispensable. Antibiotic resistance in bacterial species is regrettably a result of widespread antibiotic usage, especially abuse. The achievement of therapy is currently under jeopardy due to the sharp rise of antibiotic-resistant bacteria. Antibiotic resistance has emerged as one of the major public health concerns of the twenty-first century, according to a World Health Organisation study *(Organisation et al., 2014)*. The two primary defensive mechanisms used by bacterial cells to lessen their susceptibility to antibiotics are the suppression of enzyme activity and the effectiveness of efflux pumps. It is become increasingly difficult to treat many bacterial diseases since the existing antibiotics are no longer as effective or efficient against certain bacterial species. The significant problem of bacterial resistance to antibiotics has a productive answer thanks to nanotechnology. Effectively binding to the bacterial surface, NPs can breach the cell wall, causing more cell death *(Wang et al., 2017)*.

Less than 20 nm-sized NPs have been shown to be able to pass through the bacterial cell wall, impairing the metabolic processes and finally causing the cell organelles to break down and the bacterium to die. Natural flavonoids that block enzymatic activity that impedes the production of nucleic acids in certain microorganisms are appropriately capped on biogenic nanoparticles. It is well known that NPs produce reactive oxygen species (ROS), which physically harm the bacterial cell membrane. NPs are reportedly recyclable and may be used again as antibacterial agents. Since NPs simultaneously target many biological pathways, it is extremely difficult for bacteria to acquire resistance against NPs. Consequently, for the treatment of bacterial illnesses resistant to antibiotics, NPs can be an excellent alternative to traditional antibiotics *(Singh et al., 2020)*.

Nowadays, the production of biogenic nanoparticles has garnered significant interest due to its affordability, environmental friendliness, and relatively simple synthesis process *(Duan et al., 2015, Ahmed et al., 2017)*. Cellular extracts from living things, including plants, bacteria, algae, fungus, and actinomycetes, are used in this procedure as capping agents and green reaction medium (Akhtar et al., 2013). Because aqueous biological extracts are non-volatile and non-toxic, they have emerged as viable medium for the creation of nanoparticles. According to Sharma et al. (2019), biological extracts are a blend of many active biomolecules such as proteins, carbohydrates, vitamins, polymers, and natural surfactants that provide synthesised NPs increased stability and dispersibility. Numerous review papers on the use of biogenic NPs to prevent harmful bacteria have been published recently. Duran et al. (2016) released a review paper that concentrated on the antibacterial effectiveness of silver nanoparticles. The creation of silver nanoparticles mediated by plant extract and their application in antibacterial applications were emphasised in the review study written by Ahmad et al. *(Durán et al., 2016)*. AgNPs and Zn NPs' antibacterial activity was the primary topic of several additional publications that were also published *(Rai et al., 2012, Ahmed et al., 2016)*, figure 2.

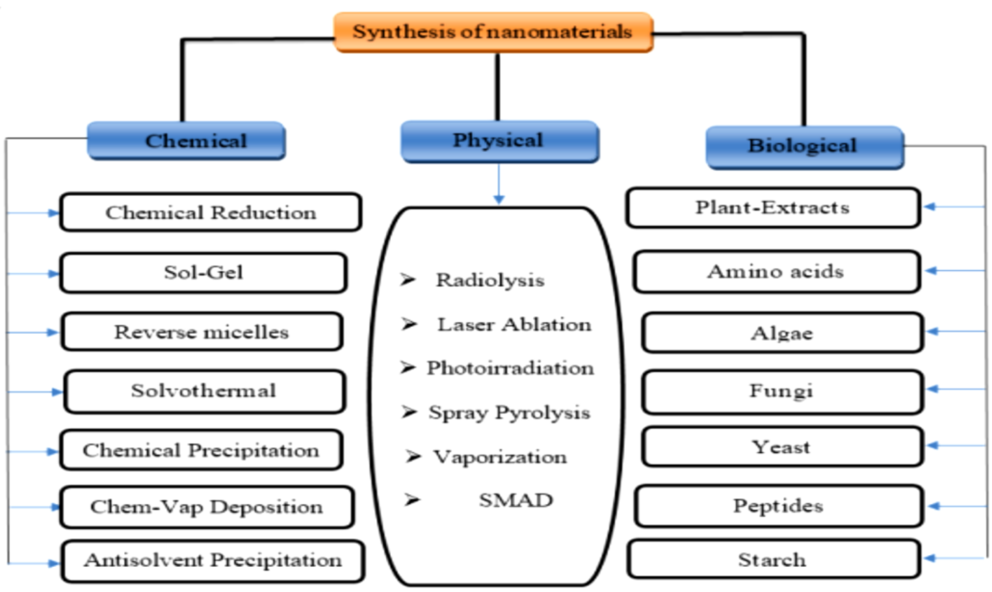

Figure 2: *(Schematic sketches of the different methods for nanomaterials synthesis (Ali, 2016).)*

Characterization of Nanoparticles

Any technique of synthesising nanoparticles must be characterised in order to determine their basic characteristics, including size, flocculation in different environments, adsorption to biomolecules, aggregation, stability, and nett charge. Regarding the application of these nanoparticles, this offers basic information. A multitude of methodologies are employed to characterise the synthesised nanoparticles. The most often employed methods include photon correlation spectroscopy (PCS), AFM, FT-IR, atomic force microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD), nanoparticle surface area monitor (NSAM), and time of flight mass spectroscopy (ATFMS), and scanning mobility particle sizer (SMPS) *(Ali, 2016)*.

The key to improving health is the application of nanotechnology in medical research to design and develop a delivery system that increases the effectiveness of APIs (Active Pharmaceutical Ingredients). When compared to traditional dose forms, these administration methods provide several benefits, such as improved effectiveness, less toxicity, and more patient compliance and convenience *(Güncüm et al., 2018)*. While these benefits may be substantial, it is also important to consider potential drawbacks, such as toxicity or non-biocompatibility of the materials utilised and undesired degradation byproducts *(Bhowmik et al., 2022)*. Reduced dosage and frequency of administration of medications combined with controlled release facilitated by biodegradable and biocompatible nanotechnology-based carriers may enhance therapeutic efficacy, reduce systemic side effects, and boost patient adherence to the regimen *(Güncüm et al., 2018)*. In comparison to other methods, the nanoparticles have a lot of benefits, such as shielding the drug contained from the pH environment, enzyme degradation, and drug efflux pump. They also need to be stable in the gastrointestinal (GI) tract. They could also have controlled release characteristics and improve medication absorption *(Pandey et al., 2005)*.

The role of gold Nanoparticles in Wound Healing

Wound healing (WH) is a very complex biological process involving a systematic series of molecular and cellular interactions designed to rebuild damaged tissue and regenerate its protective barrier purpose. The WH process is carried out concurrently in four various phases such as inflammation, proliferation and remodelling. The therapeutic agents used to treat wound infections are very expensive, toxic and hazardous to the healthy tissues around them. Thus, nanotechnology has provided new ways to build possible therapeutic agents *(Janis and Harrison 2014)*.

The basic characteristics of NPs that include shape and size together with their unique optical and thermal properties made them suitable for the treatment of wound infections. The researchers focused on finding an alternative therapeutic solution utilizing biocompatible and green methods. Usage of plants to effectively and economically prepare biogenic colloidal gold NPs *(Kasithevar et al., 2017)*. Gold nanoparticles in wound healing and repair of collagen tissues that are damaged have shown very effective antimicrobial and antioxidant activity (Volkova et al., 2016). Protein secretion. (IL8, IL.12, VEGF, TNF.α), includes gold nanoparticles, that are effective applicants for wound healing by anti-angiogenic and anti-inflammatory action *(Pivodová et al., 2015)*. Gold is regarded as a noble metal because of its inertness towards other atoms and molecules, which contributes to its high degree of biocompatibility and apparent lack of cytotoxicity to human cells. The inherent characteristics of this material have been utilised for several biological purposes, including microbe detection, biosensors, targeted medication *(Dizaj et al., 2014)*.

AuNPs can be produced through both "top-down" and "bottom-up" techniques, but green synthesis has also gained popularity due to its environmental friendliness *(Shah et al., 2014)*. Salmonella typhi, E. coli, P. aeruginosa, Bacillus subtilis, Candida albicans, and Candida glabrata are just a few of the bacterial and fungal strains that gold nanoparticles (AuNPs) effectively combat in addition to major pathogenic bacteria like S. aureus and K. pneumoniae, including AR-strains. AuNPs are more effective than AgNPs at fighting microbes when paired with antibiotics, vaccines, and antibodies. This is due to the fact that these combinations enhance the intracellular transport and diffusion of AuNPs; however, when utilised independently, their main means of causing disruption to protein synthesis *(Cui et al., 2012)*, ATP synthesis *(Nisar et al., 2019)* by inhibiting ATP-ase and damaging the microbial cell membrane, and membrane potential *(Gharpure et al., 2020)*. These NPs also seem to disrupt biofilms; however, when AuNPs are combined with proteinase-K, this impact is enhanced *(Habimana et al., 2018)*.

However, its antifungal action results from the H+ transport chain being inhibited at the plasma membrane by H+-ATPase *(Ahmad et al., 2013)*; Figure 1).

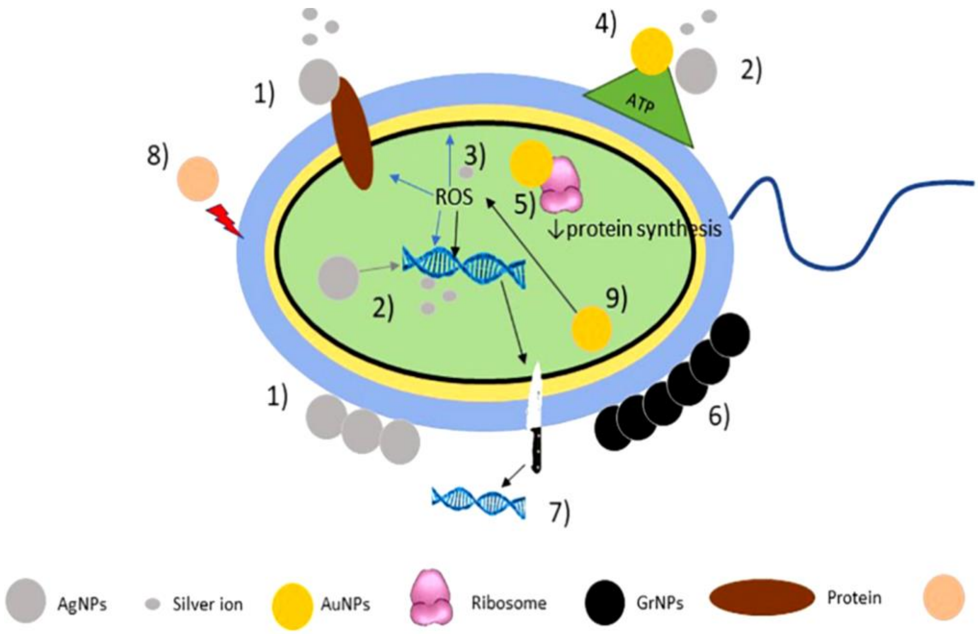

Figure 3. *(mechanisms via which nanopaticles work. AgNPs:* ***1)*** *attach to the membrane of the cell, neutralising its charge; this changes the membrane's permeability and influences respiratory chain proteins and membrane transport;* ***2)*** *release silver ions, which impact ATP production and genetic expression; and* ***3)*** *produce reactive oxygen species (ROS), which damage DNA and the membrane of the cell.* ***4)*** *AuNPs block ATP synthase;* ***5)*** *GrNPs can capture bacteria and form nano-blades that cleave cell membranes and shred DNA, whereas AuNPs prevent tRNA from attaching to the ribosome.* ***8)*** *GrONPs destroy the bacterial cell membrane; and* ***9)*** *oxidative stress that depends on ROS but is also independent of it (Gómez-Núñez et al., 2020).)*

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