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Review Article

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ROUTE OF ADMINISTRATION OF NANOPARTICLES COMBATING A RESISTANT BACTERIUM.

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ABSTRACT

In the middle of the late century, the concept of medicine has been reshaped and reformed by the discovery of antibiotics. Untreatable infectious diseases have become treatable, However, with time microbes adapt to resist the antibiotic treatments due to their enormous adaptive ability. Therefore, new antibiotics were required to combat these resistant bacteria. But the enormous adaptive ability of bacteria has turned the next generation of antibiotics obsolete. Thus, Nanoparticles play a crucial role due to their antibacterial activity. Besides, these can act as carriers for various antibiotics to increase their efficiency against superbugs. The current review provides an in-depth overview of nanoparticles, their biosynthesis, antibacterial activity, and synergistic effects with various antibiotics.

Key words: Antibiotics; Biosynthesis; Nanoparticles; Resistant Bacteria; Synergistic effects.

INTRODUCTION

The Word 'Antibiotics' means 'against life' was first used by Selman Waksman in 1941 to describe any small molecules that inhibit the growth of microbes (Agarwal & Nair, 2013; Clardy *et al*., 2009). They can be either bactericidal or bacteriostatic (Zaman *et al*., 2017). Many have perished since time immemorial from minor bacterial infections like scarlet fever, strep throat, diphtheria, syphilis, and risky surgery (Derderian, 2007), therefore the discovery of antibiotics is a blessing to mankind (Regea, 2018). 'Magic bullet' is the term used to describe "Antibiotics" because it selectively targets microbes that were liable for causing diseases but leaves the host unharmed. Which made it a miracle drug (Gradmann, 2011; Zaman *et al*., 2017). Furthermore, with the commercial availability of antibiotics to the public in the 1940s the lifespan of the people increased as the risk of dying from infection and surgeries became safer than before (Pandiarajan *et al*., 2015). The period from the 1950s to the 1970s is often regarded as the golden age of antibiotic discovery, characterized by a significant increase in the identification of new antibiotic classes. (Aminov, 2010).

In 1928 the β-lactam first natural antibiotic known as Penicillin was discovered by Alexander Fleming (Derderian, 2007; Van Hoek *et al*., 2011). The paper was published in the British Journal of Experimental Pathology (Derderian, 2007; Tan & Tatsumura, 2015). Fleming predicted the rise of antibiotic resistance against penicillin when he observed that microbes have begun to adapt against the drug (Gottfried, 2015). It is a misconception that the body has become immune but rather it is the microbes that have developed and acquired resistance within the presence of therapeutic levels of the antibiotics (O'Brien & Stelling, 1996). Thus, it makes it difficult to provide treatment with the same antibiotic against a resistant bacterium for the infected individual (O'Brien & Stelling, 1996; Zaman *et al*., 2017).

Resistance against antibiotics can be either natural or acquired by the microbes (Drăghici *et al*., 2017). For instance, a resistant microbe lacks a delivery structure for Antibiotic adhesions thus it can lack, alter, and cover its antimicrobial binding sites (Drăghici *et al*., 2017; Todar, 2011). Resistance can be acquired either by modification in its genes (Chromosomal Mediated) or by the uptake of new genes from other sources through horizontal gene transfer (Todar, 2011). The transfer of antibiotic-resistant DNA from parent to offspring is referred to as vertical gene transfer or vertical evolution (VGT) (Drăghici *et al*., 2017., 2017; Todar, 2011). Whereas bacteria can also acquire resistant determinates via

horizontal gene transfer (HGT) including direct uptake of Deoxyribo Nucleic Acid (DNA) from decay bacteria (Transformation), bacteriophage transmission (Transduction), and physical contact with other bacteria (conjugation) (Lin *et al*., 2015). The transfer of DNA can occur between the same or different bacterial species (Todar, 2011).

Even though the availability of antibiotics is a blessing, it can be argued that it is also the reason for the rapid development of antibiotic resistance (Butler *et al*., 2006). Throughout the globe microbes are developing resistance against antibiotics at such a rapid pace that no proper countermeasure has yet been developed, therefore, the world may return to the post-antibiotic era where death from trivial infections may once again become commonplace (Shrivastava *et al*., 2018). Thus, society must contribute to the development of new antibiotics to scale back the mortality rate (Lenski, 1998).

With each new resistant strain against existing antibiotics identified (Kyriacou *et al*., 2004) indicates that the development of new bactericides should be crucial (Sondi & Salopek-Sondi, 2004). Therefore, it is important to take steps for the preservation of antibiotic effectiveness to use the mention of drugs for both animals and humans (Dugassa & Shukuri, 2017).

Several classes of nanoparticles and the nanosized carrier have novel antimicrobial effective against resistant pathogens. Antimicrobial effect proves by testing it in the lab on models against organism against resistant pathogens (Huh & Kwon, 2011a).

Depending upon the formation of Nanoparticles, Nano-capsules and Nanospheres the antimicrobial drug can be diffuse, trapped, covered, or attached to the nanoparticles can be obtained. Nano-capsules structure contains a drug that is congested in a matrix-bound by a polymeric sheath, while the drug is uniformly scattered in the nanosphere matrix (Mohanraj & Chen, 2006).

Nanoparticles offer the platform to assign various duplicates of therapeutic agents on it, hence, it can increase the concentration of therapeutic and diagnostic agents at the pathological site (Mody *et al*., 2010). To better transmit the antibacterial effects, nanoparticles provide a broader scope of interactions between organic and inorganic molecules (J. S. Kim *et al*., 2007). Thus, Broad-spectrum antibacterial NPs agents have been established for Gram+ve and Gram-ve microbes. For example, Zinc Oxide Nanoparticle (ZnO) were identified to inhibit E. coli, S. aureus, and P. aeruginosa. whereas Gold (Ag) Nanoparticle displays concentration-dependent antibacterial action against *Pseudomonas aeruginosa* and *E. coli* (Ramalingam *et al*., 2016).

Furthermore, Nanoparticles which includes Palladium (Seshadri *et al*., 2011), selenium (Skalickova *et al*., 2017), Graphene (Wainwright *et al*., 2017), gold, Carbon-tubes, platinum, silver, titanium, thallium, cerium, iron, copper, and zinc (Elizabeth *et al*., 2019; Sánchez-López *et al*., 2020) and it's composite (E.g., fluoride, chloride, sulfides, hydroxide, phosphate, and oxides) (Elizabeth *et al*., 2019). Thus, it gives preferable remarks in combination with penicillin (Raja & Singh, 2013), oxytetracycline (Abo-Shama *et al*., 2020), ceftazidime (Arora *et al*., 2015; Isaei *et al*., 2016), and antibiotics with furthermore Nanoparticles (Gu *et al*., 2003; Jesline *et al*., 2015; Nene *et al*., 2019).

The review is conducted to understand the synthesis, antibacterial, and synergistic effects of different nanoparticles with a diverse class of antibiotics against resistant bacteria. This study also provides recent updates about nanotechnology which helps to develop and design an alternate treatment against superbugs infections to limit the usage of antibiotics in the future.

Antibiotic Resistance and Its Consequences: Antibiotics are the pillar of medicine and are utilized worldwide on huge scales (J. Blaser, 2016; Odonkor & Addo, 2011). There is a reduction in the death rate of infected patients and a change in the diseases and surgical procedures (Hirsch, 2008). Treatment to antibiotics and cure of the infection which decreases the case of infection, it has improved the life quality of the infected patients, decreasing infantile death, increasing life span, and saving various life (Helen *et al*., 2013). Antibiotics are essential to compete against an infectious disease which is caused by microorganisms from the past few years, the antibiotics resistance is growing faster than it is controlled (Odonkor & Addo, 2011). Few microorganisms are resistant to some antibiotics, and they can only be treated with experimental and highly toxic drugs (David L. Cohn, 1997). Generations of antibiotics development have depending on evolving MDR and their mode of resistance. The commonly known antimicrobial mechanism of antibiotics includes inhibition of enzymes, interference in Deoxyribo Nucleic Acid (DNA), Ribo Nucleic Acid (RNA), and protein synthesis, and distraction of membrane structure (Kohanski *et al*., 2010).

Due to antibiotic resistance globally 700,000 individuals lose their lives (Friedman *et al*., 2016) more than 2.8 million infections were caused by antibiotic-resistant pathogens in the United States annually, 35,000 deaths have been reported according to a Centers for Disease Control and Prevention (CDC) report (Prestinaci *et al*., 2015). The resistance to drugs like tuberculosis, typhoid, and gonorrhea causing high costs to individual health in addition to the health care system due to their increasing every year in developing countries (Annavajhala *et al*., 2019; Bassetti *et al*., 2019; Ramírez-Castillo *et al*., 2018). Now about 4.1% of new cases of tuberculosis are known as multi-drug resistant (Llor & Bjerrum, 2014). Following

countries have a higher number of TB cases like India, Russia, South Africa, and the Philippines as compared to other countries (Chatterjee *et al*., 2018).

Antibiotic Mode of Action: Antibiotics are molecules that can directly inhibit the growth of microorganisms (Scheffler *et al*., 2013). Penicillin was the first invented antibiotic. After the invention of penicillin, many other antibiotics were discovered, and due to which mostly infectious diseases become under control. The antibiotics are classified based on their chemical structure, their mode of action, and (Adzitey, 2015). Antibacterial action has five mechanisms. A lot of Which cellular functions targeted by antibiotics are effective given below (Carman & Wilkins, 1991)

•Cell wall synthesis inhibition
•Inhibition of cell membrane
•Structural and functional inhibition of nucleic acid
•Protein synthesis inhibition
•Metabolic pathways keys blockage

Different Mechanism of Antibiotic Resistance: The antibiotics resistance of infections occurs when there is an increase in frequency with effective treatment of Animals and Humans. The antibiotic resistance has increased due to their exposer to an environment. Different physiological and biochemical mechanisms are responsible for antibiotic-resistant development. The mechanism of resistance is developed from genetically inherent or can be result when microorganism become exposed to antibiotics. Most of the antibiotic resistance has developed from the result of mutation or by transfer of genetic material between microorganisms from different process. The antibiotic resistant may lead to increased mortality rate, morbidity rate, costs of treatment, and loss of production in animals. From the 1990s, few strains of *Salmonella* became resistant to the number of antibiotics. The problem in the clinical practice today is the multiple-drug resistance, which is resistance to several types of antimicrobial agent. Speciously most pathogenic microorganisms have the ability of developing resistance to some antimicrobial agents. Some resistant mechanisms are (C Reygaert, 2018).

•Target site modification
•Modification of enzyme
•Efflux pump modification and transfer of plasmid
•Formation of biofilms
•Swarming

Types and Characterization of Nanoparticles: Nanoparticles are divided into different classes, based on their size, morphology, and chemical property including ceramic-based NPs, Metallic NPs, Lipid-based NPs, Semi-conductor NPs, Polymer-based NPs, Magnetic NPs, and Carbon-based NPs (Zain *et al*., 2022; Bhatia & Bhatia, 2016; Saeed & Khan, 2016).

Carbon Nanoparticles: Carbon NPs were classified into two groups such as fullerenes and carbon nanotube. While fullerenes form of carbon NPs is discovered in 1985, and it contains 60 or above carbon molecules and it has a hollow cage shape (Astefanei *et al*., 2015). Although, the 60-carbon arrangement is termed as Buckminsterfullerene, while carbon atoms are arranged in Penta or hexagonal form and are 7 Å in diameter, and its shape is as like hollow football. Fullerenes-based carbon NPs are of different types such as endohedral fullerenes, Alkali-doped fullerenes, endohedral metallofullerenes, heterofullerenes and exohedral fullerenes (Bhatia & Bhatia, 2016). Thus, all types have commercial importance because of their structure, high potency, electron affinity, flexibility, and good conductivity (Astefanei *et al*., 2015; Ma & Liang, 2010). besides, these fullerenes are less soluble in natural solvents (Chakravarty & Kivelson, 1991), representing them as a most useful strategy in disease diagnosis, imagining, and drug transport (Bosi *et al*., 2003).

Carbon nanotubes (CNTs) are 1-2 nm in diameter and are cylindrical while the graphene layer is rotated in the CNT which has great importance. These sheets can be single terms as single-walled (SWNTs), double layer sheet called double-walled (DWNTs), and multi-walled carbon nanotubes (MWNTs). Thus, MWNTs' diameters range up to 10 nm, but length varies from 1μm to few micrometers (Reilly, 2007). while there is a gap of 0.36 nm among each sheet depends on the number of a divider in the structure (Bhatia & Bhatia, 2016). CNTs' lengthways are conductor but through the tube is nonconductor and it can be produced through the Chemical Vapor Deposition (CVD) method (Elliott *et al*., 2013). Due to outstanding physical, chemical, and mechanical features Carbon Nanotubes (CNTs) has a broad range of functions in environmental remediation (Ngoy *et al*., 2014), maintain the standard for distinctive inorganic and natural facilitators (Mabena *et al*., 2011). Although Carbon-based nanoparticles have widespread functions in bioscience such as gene silencing, diagnostics, reduced toxicity, and increases efficacy, additionally used in drugs, gene, and protein transport (Bhatia & Bhatia, 2016).

Ceramic-based NPs: Ceramic-based NPs is consisting of carbides, phosphates, oxides, and carbonates of different metals and metalloids like titanium, calcium, silicon, and so on. That has been discovered in amorphous, polycrystalline, dense, porous, or hollow structures (Thomas *et al*., 2015). It is smaller in size about <50 nm (Cuenca *et al*., 2006). Ceramic-based NPs can be used for many purposes in the biological field such as drugs, proteins, genes, and imaging source carriers. Several bacterial infections were treated by using ceramic-based NPs including glaucoma (vision loss) caused by rapid immune responses when exposed to

microbes, ceramic NPs were used as drug transporter to the infectious site, and so on (Thomas *et al*., 2015).

Metallic NPs: These nanoparticles are produced from metals through chemical, electrochemical, and photochemical approaches (Khan *et al*., 2019). Metal-based NPs have several uses like anticancer agents, Targeting, molecular imaging, and drug transporter. AgNPs can be used in chemotherapy, radiosensitizers, diagnosis, carrier, transfection vectors, and antiviral agents. Cu NPs have been widely used for industrial purposes especially in the pharmaceutical industry (Thota *et al*., 2017).

Semiconductor Nanoparticles: Semi-conductor NPs have characteristics of both metallic and non-metallic compounds (Ali *et al*., 2017; Khan *et al*., 2017). That lies in group-IV of the periodic table (silicon, germanium, tin), group-VI (selenium, tellurium), groups-III-V (Gallium, arsenic), group-V (mercury, indium, telluride), groups-II-III-V (aluminum, gallium, arsenide) (Khan *et al*., 2019). The luminescent thing of semiconductor NPs resides in the center of the inorganic semiconductor. Although nanocrystals of semiconductors are termed as quantum dots and it has zero dimension while size ranges about 2-10 nm, for example, ZnS is used to improve the optic properties while CdSe is an improved aqueous organic shield (Bhatia & Bhatia, 2016). Both are used in electronic devices, photocatalysis, water splitting as well as photo optic. They were used as a probe to label different tissues, cells, etc (Walkey *et al*., 2009).

Polymer-based NPs: These are commonly organic-based NPs (Khan *et al*., 2019), even though polymeric NPs, nanostructures are made up of natural or artificial polymers (Pécurto Cartaxo, 2018). Thus, the polymeric structure design for NPs are degradable and non-hazardous. PNP is very important in the field of medical sciences, used as gene carrier and drug transporter to specific tissue or organ furthermore used to control the release of the therapeutic agent on their targeted site (Chevalier *et al*., 2015; Mallakpour & Behranvand, 2016).

Kumar acknowledged the formation of decomposable polymeric NPs for the transport of quercetin drugs. Furthermore, the decomposable polymer used is poly-ε-caprolactone (PCL). This is non-hazardous, decomposable, and biocompatible, and is ratified by the FDA. These NP can be used furthermore, in drug companies as a controlled release of the drug on the infectious site (Dinesh Kumar *et al*., 2015).

Lipid-based NPs: They are usually 10 to 100nm in diameter and are globular in structure. The inner part of lipid NPs is made up of lipid while the medium contains soluble lipophilic particles. Whereas surfactants and emulsifiers are used to maintain the exterior shall of lipid-based NPs (Khan *et al*., 2019). In the area of nanomedicine, lipids such as phospholipid-based drug transport method are the most investigated platform, because of their flexibility, biocompatibility, biodegradability, and non-hazardous characteristics (Joshi & Müller, 2009; Kohli *et al*., 2014; Puri *et al*., 2009; Stylianopoulos & Jain, 2015; van Hoogevest & Wendel, 2014). Thus, different lipid cores have been proposed for the transport of lipophilic and hydrophilic agents from distinctive routes of administration (Miranda *et al*., 2017; Puri *et al*., 2009). Furthermore, liposomes are considered the first batch of lipid nanocarriers (Bulbake *et al*., 2017). Liposomes are considerably used due to their extraordinary level of biocompatibility and their ability to encapsulate a broad range of cargos (García-Pinel *et al*., 2019). Lipid NPs has wide range uses in a bio-medical field such as Drug carrier, transporter and it controls the release of RNA in cancer treatment (Khan *et al*., 2019).

Magnetic NPs: This NPs size is less than 100nm and it can only be operated under magnetic area/range. Magnetic NPs are made up of two elements, magnetic substance (cobalt, nickel, iron, and their oxides are magnetite, maghemite, cobalt ferrite, and chromium dioxide) and chemical compounds. While the characterization of these compounds was fully based on magnetic sensitivity, either for diagnosis or therapeutic reasons. Although magnetic NPs are used in cancer therapy termed magnetic hyperthermia. Furthermore, paramagnetic Fe2O4 NPs are used in magnetic resonance imaging (MRI) whereas, it identifies the target organs and tissues (Cuenca *et al*., 2006).

Table 1: Nanoparticles Classification & Characterizations

Biosynthesis of Nanoparticles: Both land and marine plants, and animals with their extracts along with various enzymes, micro-organisms, fungi, and algae are used to produce NPs.

NPs synthesized by bacteria: Culture the isolated sample of *K. pneumoniae*, *E. coli*, and *P.jessinii* overnight on the following media; (Nutrient broth, Sharpe broth, AgNP nutrient broth, lysogeny broth, Mueller Hinton broth) grow at 30 °C for 18 h. For the determination of MPN of bacteria, dilute the overnight bacterial culture about 10 folds in Quarter-strength Ringer's Sol then, pour and spread the diluted sample on STI-agar now let the bacteria to complete its growth period in an incubator for 18 h at 30°C. For the synthesis of silver nanoparticles, 1st centrifuge the remaining overnight culture 3220g for 15 min then filtered the supernatant by using 0.2 µm filter. 2nd Add 200 µl of supernatant, 200 µl of the control (uninoculated culture media), or the solution of individual components, on 20 ml of 1 mM $AgNO_3$ aqueous solutions. 3rd step is to incubate the mixture at room temperature in normal daylight. Whereas the development of AgNPs can be classified by UV-Vis analyses or DLS. Thus, the formation of the silver nanoparticle can be determined by SEM and EDX (Müller *et al*., 2016).

NPs synthesis by Fungi: Nanoparticles Sb_2O_3 were prepared by using baker's yeast. Grow yeast cells in the presence of carbon and nitrogen source as suspension culture for 36h. filter and dilute 25ml of suspension culture for 4 times then add 30% Et-OH containing nutrient and incubate it for 24h till it becomes light straw. Now add 20mL (0.025M) of SbCl3 in the cultured solution and heat it on the stream of water at 60°C for 10–20min until precipitation appears on the bottom of the tube, which indicates the initiation of transformation. The sample was allowed to cool and incubate at room temperature. After 3-4 days cluster deposition can be observed in the bottom of the tube and can in pH were also observed in this stage. The formation of Sb_2O_3 nanoparticles was checked by XRD and TEM (Jha *et al*., 2009).

NPs Synthesis by Plants: Silver nanoparticles can be synthesis from various parts of the plant such as (leaves, bark, and root) of Avicennia marina mangrove plant. 1st wash the sample with tap water to detach all the impurities and contaminants. Then Cut 10g of plants' various parts into small pieces then boil it in 100ml distilled water for 5min, filtered the extract. Treat 10ml of filtrate with 90ml of $AgNO_3$ sol and incubate it at room temp for 10min. the formation of brownish-yellow color indicates the formation of AgNPs (Gnanadesigan *et al*., 2012).

NPs Synthesis by Algae: Gold Np can be synthesized by seaweed (marine alga) like *S. wightii*. 1st Wash the sample with tap water followed by distilled water lets the sample for 3-5 days to dry completely. Thus, convert the dried sample into powdered form then stored it in a glass. Whereas we use chloroauric acid ($HAuCl_4$) as a precursor. For the synthesis of Au add 1g of powdered seaweed in 100mL of 10-3 Molar aqueous solution of $HAuCl_4$.Thus, under stirring conditions removal of $AuCl^{-4}$ ions will take place within 12h. thus, remove the residue from the reaction mixture while light immersions can be observed under UV-spectrophotometer. Whereas after 15h of incubation the color of the medium turns into ruby red can be observed by visual observation (Singaravelu *et al*., 2007).

Table 2: Synthesis of Natural Products from Precursors in Specific Samples.

Nanoparticles And Their Antimicrobial Activity: A promising strategy for dealing with bacterial resistance is the mixture of antibiotics with nanoparticles. These combinations inhibit the increase of pathogenic microorganisms, along with resistant bacterial strains, at very low concentrations (A. *et al*., 2009; Darroudi *et al*., 2014; Kvítek *et al*., 2008). NPs are minute but strong material with at least one dimension between 1 and 100nm (Narayanan & Sakthivel, 2010; K. Roy & Ghosh, 2017).

Drug resistance is much weaker with the antibiotics comprising nanoparticles because it directly comes into the contact of bacterial cell wall without the need to integrate into the cell. Thus, NPs uplift the expectation that it will be less susceptible to boost the microbial resistances then drugs (Knetsch & Koole, 2011). Therefore, researchers pay full interest in new and exciting NP-based substances along with their antibacterial properties (Wang *et al*., 2017).

NPs exhibit broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. For instance, ZnO NPs show antibacterial activity against *S. aureus*, while Silver nanoparticles exhibit concentration-dependent antibacterial activity against *E. coli* and *P. aeruginosa* (Edmundson *et al*., 2013; Wang *et al*., 2017). TiO2 can exert a bactericidal effect in opposition to *Pseudomonas aeruginosa*, *Enterococcus hirae*, *Staphylococcus aureus*, and *Bacteroides fragilis* (Ayaz Ahmed *et al*., 2016).

The key methods for the antimicrobial action of NPs are, interference with the bacterial cell-membrane; Formation of Reactive Oxygen Species (ROS), integration of bacterial plasma membrane, and intracellular induction of antibacterial effects which consists of the interplay between DNA and proteins (Wang *et al*., 2017).

The testing of the antimicrobial effect of NPs proved that some NPs have an antibiofilm mechanism, which includes Au NP (Q. Yu *et al*., 2016), Ag NPs (Markowska *et al*., 2013), Mg NP (Lellouche, Friedman, Lahmi, *et al*., 2012), Nitric-oxide NPs (Hetrick *et al*., 2008; Slomberg *et al*., 2013), ZnO NPs (Hajipour *et al*., 2012), CuO NPs (Miao *et al*., 2016), Fe_2O_3 NPs (Chifiriuc *et al*., 2012) and YF_3 NPs (Lellouche, Friedman, Lahmi, *et al*., 2012).

Greater prevention of biofilms formation (L. Zhang *et al*., 2010) can be gained by using NPs of smaller size that has antibiofilm activity thus the particle shape may also have a great impact on biofilm eradication (E.g. Rod-shaped NPs are more potent than spherical shape NPs) (Slomberg *et al*., 2013). According to previous research, hydroxyapatite whisker and nano-zinc oxide (HAPw/n-ZnO) complex show great antibacterial activity against, *Candida albicans*, *E. coli* and *S. mutans* (Wang *et al*., 2017).

According to Tu *et al* (2016) graphene nanosheet shows antimicrobial effect against *E. coli* (Tu & Fang, 2016). Akhavan and Ghaderi investigated the interplay of the bacterial plasma membrane with graphene nanosheets. Specifically, the complete dampening of graphene via membrane lipids in water. Dispersive adhesion is a vital role performed via the interplay between the graphene and lipids during extraction (Akhavan & Ghaderi, 2010). whereas Ansari also investigated that Al_2O_3 NPs coves the plasma membrane. As a result, membrane permeability is lost due to the production

of oxidative stress (Ansari *et al*., 2015).

NPs can introduce ROS in microbes by way of diffusion. Thus, graphene oxide (rGO) -iron oxide NPs complex causes physical and chemical damage to the bacterial cell by producing •OH radicals that diffuse throughout the cell, and thus inactivates MRSA (W. Y. Pan *et al*., 2016). while CuO NPs can alter the appearance of important proteins. According to proteomic bioinformatics analysis once CuO NPs integrates the cell will, will alter the expression of proteins that are involved in nitrogen metabolism, or electron and material transports (Su *et al*., 2015).

Research proves that Iron-oxide NPs can generate ROS that interferes with the cofactor (NAD) of bacterial metabolism (Niemirowicz *et al*., 2014). super-paramagnetic Fe_2O_4 can harm the larger molecules (DNA, lipids, and proteins) once entered in the cell through Fenton reaction (catalytic process converts H_2O_2 into •OH) that leads to bacterial death (Bajpai & Gupta, 2011; Hajipour *et al*., 2012; Niemirowicz *et al*., 2014). Besides this NPs can alter the functional protein of the bacterial metabolic pathway. Whereas CuO NPs can alter the protein expression of the nitrogenous metabolic pathway of bacteria and thus can halt the function of nitrate and nitrite reductase enzymes (Su *et al*., 2015). TiO2 can control bacterial biofilm formation. Besides, these NPs can also determine the bacterial metabolite level (Peng *et al*., 2013; Roguska *et al*., 2015). For biofilm-forming bacteria, metabolism is one of their prime events (F. Pan *et al*., 2015). Therefore, D-ala metabolism is necessary for the development of S. mutans (Qiu *et al*., 2016).

Quorum sensing in biofilm-forming bacteria was accomplished through a potassium ion channel (Lundberg *et al*., 2013). Moreover, potassium ions dispersion set off the metabolic activities of biofilm-forming bacteria from inner and outer portion. Mg NPs also can stay and dispersed inside the biofilm, hence causes disturbance in DNA binding, membrane potential gradient, and boost lipid peroxidation. To reduce the bacterial biofilm-forming capability some disturbance and changes are necessary for the proper functioning of the cell process (Wang *et al*., 2017). However, research proves that NPs can exploit the ion channels of biofilm-forming bacteria. Thus, the mechanism of action of NPs against biofilm-forming bacteria is like the regulation of bacterial metabolism. Whereas the major target of NPs is the metabolic pathways (Lellouche, Friedman, Gedanken, *et al*., 2012).

Yttrium Oxide ($Y_2O_{3)}$ NPs Show broad-spectrum antimicrobial activity against *Pseudomonas desmolyticum* and *S. aureus* due to its prism shape. Whereas the shape of Y_2O_3 NPs increases its antimicrobial activity which allows it to adhere to the bacterial plasma membrane. Thus, leading to the breakdown of the plasma membrane (Wang *et al*., 2017). Although, research shows that many NPs have antimicrobial activity and their targets are the main process and molecules of the bacterial cell, like Bacterial metabolic pathways and their co-factors, Ion channels, Plasma membrane, Electron transport chain, and many more.

Synergistic Effect of Nanoparticles With The Combination Of Antibiotics Against Resistant Bacteria: There is a quick increase of resistant bacteria that are occurring throughout the world, it has endangered the usefulness of antibiotics which has always played an important role in saving millions of lives (Golkar *et al*., 2014). There are several reasons behind the antibiotic resistance crisis which include misuse and ill-use of medicines, in addition to this the pharmaceutical industries due to some economic reasons have led to the deficiency of new medication development (Michael *et al*., 2014). Therefore, there is a great need for struggles to devise new strategies, renew research efforts, and chase steps to cope with the calamities (Gould & Bal, 2013). Due to the capability of microorganisms that they can beat and surpass the most effective and new generation antibiotics due to the development of resistance, consequently, there is an immediate need of developing novel antibiotics and therapeutics to cope with the infection caused by bacteria. In today's world, the great healthcare challenge faced by humanity is the increasing occurrence of antimicrobial resistance due to pathogenic bacteria (Burke, 2003). Using nanomaterials with antimicrobial activities is the best way for this worldwide problem (Vazquez-Muñoz *et al*., 2019). Nanoparticles (NPs) have the potent to penetrate the cell membrane of pathogenic microorganisms and thus restrict important molecular pathways, as result formulate distinctive antimicrobial mechanisms. By the combination of NPs with some ideal antibiotics, NPs have established synergy and may help in limiting the global crisis of emerging bacterial resistance (Lee *et al*., 2019). Moreover, NPs as compared to antibiotics are less susceptible to provoke resistance among bacteria (Natan & Banin, 2017).

Nanomaterials have the capability to enter the bacterial cell and increases the antibiotic activity of the molecules which are being carried thus the bacterial resistance has been compromised. Furthermore, it has been extensively reported that NPs as carriers of commercially available antibiotics help in enhancing the antimicrobial actions and lowering the toxicity (Huh & Kwon, 2011_b). The systematic details of these nanoparticles that carry antibiotics are still unclear. However, many investigators have reported that nanoparticles may help to increase and improve the internalization of antibiotics inside the cells of bacteria and employ certain polyvalent and synergistic effects (Zhao & Jiang, 2013).

Due to the attachment of AgNPs to the bacterium surface, the cell membrane properties are

being changed. Moreover, AgNPs can cause DNA damage. They are also involved in releasing silver ions, these sliver ions reveal their antibacterial activity while interacting with the protein which is containing thiol, and as a result, its function is damaged (Durán *et al*., 2010). The same activity can be seen towards *staphylococcus aureus* and methicillin-resistant *S. aureus* with AgNPs of spherical and triangular shapes. the advantages of combining AgNPs with antibiotics has been explained and described in many studies (Natan & Banin, 2017). According to Mcshan and colleagues, there is an improved result when an ineffective antibiotic is combined with AgNPs against drug-resistant bacteria *Salmonella typhimurium* DT104 and it had an improved result in their efficacy. Combining neomycin or tetracycline with AgNPs has been observed to inhibit the growth of the *Sa. typhimurium DT104*. Furthermore, it was also found that the combination of AgNp with an antibiotic has no toxicity to human skin cells which suggests its potential use in treatment of infection that is caused by *Sa. typhimurium DT104*. Likewise, numerous other antibiotics has been combined with AgNPs and testified which as a result shows synergy against *S. aureus*, *E. coli* and *P. aeruginosa*. Furthermore, some other improved antibacterial activity against multidrug resistant by combining of AgNPs with antibiotics has been explored such as β-lactamase and carbapenemase-producing *Enterobacteriaceae* below the MIC concentrations of either the nanoparticles or antibiotic component of the combination (Panácek *et al*., 2016; Panáček *et al*.,2016; McShan *et al*.,2015).

Newly, by combining the amoxicillin, ampicillin, and chloramphenicol with AgNPs and development of synergistic effect- has been described (Fayaz *et al*., 2010). According to some research, the mechanism of action of the nanoparticles combined with antibiotic recommended that the development activity of antimicrobial might be because of the reactions takes place chemically, however, the fundamental molecular mechanism of the effect, either synergistic or antagonistic, still needs explanation (Li *et al*., 2005).

AgNPs-combination with Kanamycin (Km) and chloramphenicol (Cm) exhibited a synergistic effect for *E. coli*, *S. Typhimurium* and *S. aureus* with sub-lethal concentrations. As predictable, TEM analysis also showed cellular damage due to the above combination which validates MIC assays and presents an indication for the death of the bacterial cell (Vazquez-Muñoz *et al*., 2019). The membrane damage of the Gram-negative is the best explanation that represents that the Ag nanoparticles got bactericidal property after combining it with Cm or Km. Furthermore, Due to the property of Ag nanoparticle and $AgNO_3$ to depolarize and destabilize cell membrane and results in the bactericidal effect suggest that they can have microbicidal properties (Novo *et al*., 2000).

Against pathogenic bacteria, the synergetic effect of Ag nanoparticles in combination with antibiotics has been examined using the agar disk diffusion method, and the effect of antibiotics was observed to increase in most of the cases. There was an increase in the zone of inhibition against seven pathogenic bacteria due to a rapid and fast increase in synergistic interaction of AgNPs and streptomycin. Also, a comparable synergistic effect being observed When the AgNP was combined with tetracycline, Amikacin, Kanamycin, and Cefotaxime. Moreover, there was an increase in the zone of inhibition almost 6.1-fold against *E. coli*, S. *epidermidis*, and *B. subtilis* when AgNPs was combined with Cefepime. Before the group of bacteria which includes *B. subtilis*, S. *marcescens*, *Klebsiella pneumonia*, *S. typhimurium* and *E. coli* were used to be resistant to the antibiotics such as ampicillin, vancomycin, and cefotaxime, cefepime and kanamycin but later they all were inhibited when the Ag nanoparticles were used in combination with all these antibiotics. The improved efficacy of antibiotics due to Ag nanoparticles were determined, thereby, the combined use of AgNPs with certain antibiotics is of best choice against resistant bacteria (Jyoti *et al*., 2016).

By comparing gold nanoparticles with others due to their low chemical reactivity it is thought to be highly inert and non-toxic (Natan & Banin, 2017). An enhancement in the antimicrobial activity of the materials was observed after the combination of the gold nanoparticles. The example includes the formation of nanocomposite after combining Au nanoparticles with N-acylated homoserine lactonase proteins (AiiA AuNPs) with the ability to prevent biofilm formation against Proteus species which are multidrug-resistant bacteria as compared to N-acylated homoserine lactonase proteins only, moreover, there is no toxicity association to macrophages (Vinoj *et al*., 2015). Likewise, there was a boosted effect in antibacterial activity of the microbubbles by combining the gold nanoparticles to the shell of PVA-lysozyme microbubbles (Mahalingam *et al*., 2015). There is no significant cytotoxicity documentation of gold nanoparticles in the human dermal fibroblast model validating prior studies (Hwang *et al*., 2012).

TiO_2 effect alone has been observed to be low, but as it was combined with the antibiotics then obvious differences were revealed. There was a certain increase in inhibition zone when combined with following antibiotics and had the following increase and enlargement in the inhibition zone: with ampicillin and gentamycin 9 mm enlargement in the inhibition zone, in combination with amoxicillin was 7 mm increase, with erythromycin and clindamycin 6 mm and lastly, with tetracycline there was about 5 mm (Jesline *et al*., 2015).

Copper oxide (CuO), Iron oxide (Fe_3O_4), zinc oxide (ZnO), magnesium oxide (MgO) and titanium oxide (TiO_2), The metal oxides which are most commonly are being studied they all contain antibacterial and microbial activity and are being used for several purposes according to clinical points of view (W. Jiang *et al*., 2009). The antimicrobial activity of most of the metal oxides is exhibited through the generation of ROS, which is credited to intrinsic photocatalytic activity (Singh *et al*., 2014). To solve the problem that is arising due to bacterial resistance some new reviews have broadly defined the potential of metal oxide NPs to function as antibiotics (Chen *et al*., 2014).

Today one of the major nanoparticles is the ZnO NPs and per year there are about 30,000 tons of its productions (Keller & Lazareva, 2013). besides their ability they inhibit the growth of microorganisms, they are also used in cosmetics, gas sensors, pharmaceuticals, and optoelectronics like fields (Cao & Cai, 2008). ZnO NPs not only got antimicrobial activity against planktonic bacteria but rather they are also able to prevent the formation of biofilm (Hsueh *et al*., 2015; Sarwar *et al*., 2016). Both Ag nanoparticle and ZnO NPs are recognized to disturb bacterial membranes, whereas at a very low concentration Ag nanoparticles are effective as antimicrobial agents and don't possess toxicity to eukaryotic or human red blood (Krajewski *et al*., 2013). The unique and more efficient properties of the ZnO, such as being selectively toxic to biological systems inspire their possible use as diagnostics, therapeutics, surgical devices, and antimicrobial methods (Jahanshahi & Babaei, 2008; Zarrindokht Emami-Karvani, 2012). Moreover, using ZnO NPs by combining them with aminoglycosides, beta-lactams, and cephalosporins generate enhanced outcomes against various bacteria which are pathogenic (A. Roy *et al*., 2010). There are several reasons behind the Synergistic effect and results due to inhibiting the biofilm formation, the generation of hydroxyl radicals, by altering the protective cellular functions. As it is well known that the antibiotics alone doesn't have an effective function in clinical practices as compared to combining them with NPs. These combinations play an important role in reducing bacterial resistance development, and treatment time is also reduced and more importantly reduction in the antibiotic dose requirements (Hwang *et al*., 2012). When the azithromycin, cefotaxime, cefuroxime, Fosfomycin, chloramphenicol was combined with the ZnO nanoparticles and increased antibacterial action was observed, and the combination of ZnO-NPs with oxytetracycline used against Staph. aureus has improved effect as compared to antibiotics used alone. An increase in antimicrobial activity For *Salmonella* has been observed as compared to antibiotics only such as Oxacillin, Cefuroxime and Fosfomycin (Abo-Shama *et al*., 2020).

Still the mechanism of action of ZnO-NPs is not clear. But the previous studies have shown generation of ROS as hydrogen peroxide H_2O_2 can be the reason behind their bactericidal or bacteriostatic action which results in the damage of the cell wall and cell membrane and ends with facilitating entrance of ZnO-NPs due to loss of proton stimulus force (Xie *et al*., 2011).

Concentration, size, and stability are major factors behind the antimicrobial activity of the ZnO NPs (Al-Holy *et al*., 2006). According to a report Imipenem had increased antibacterial activity against *K. pneumoniae* when used in combination with zinc oxide nanoparticles (American Psychological Association, 2017).

There is also an increase in the antibacterial activity of Cu NPs in combination with antibiotics like (ampicillin, amoxicillin, gentamycin, and ciprofloxacin) (Nene & Tuli, 2019).

Nanoparticles against Resistant Pathogens: Mostly bacteria but some other pathogens are resistant to many antimicrobial agents which is alarming to scientific society and having severe health problems, many studies are carried out to improve the antimicrobial methods. More than 70% of bacteria that causative agent of poisoning and other infections is resistant to different antimicrobial agents which are used to treat mostly the infection of poisoning. The development of new antimicrobial agents results in superior power and influences. There are some nanoparticles such as copper, silver, gold, platinum, graphene oxides, nickel oxide, titanium, zinc, nitric oxide, selenium etc. these all have antimicrobial activity, some of them have broad-spectrum activity then others and these are being used from decades (Khezerlou *et al*., 2018).

Silver nanoparticles (Ag NPs) have a biocidal effect therefore it is well known and used worldwide against microorganisms from past decades it is being used to treat a various infection (C. Fan *et al*., 2016).

Silver NPs are mostly used against fungi (as antifungal) (K. J. Kim *et al*., 2009), and some have antiviral properties (Lara *et al*., 2010), and inflammatory as well (Nadworny *et al*., 2010) due to their inaccessible physical and substance properties and high surface region to volume proportion Ag NPs are used against multidrug resistant bacteria as antimicrobial agent (Loo *et al*., 2018). Silver NPs are powerful against both Gram-positive and Gram-Negative microscopic organisms due to their size of 10-100nm (Morones *et al*., 2005). The micro size of Ag nanoparticles helps them for the attachment to the cell wall and then easily penetrate to cell, where it improves their antimicrobial activity against bacteria (Loo *et al*., 2018). Ag NPs are effectively used against *Escherichia coli* (Paredes *et al*., 2014), *Staphylococcus aureus* is a methicillin resistant (MRSA) (Paredes *et al*., 2014; Yuan *et al*., 2017),

and against bacteria which produces extended spectrum beta-lactam (ESBL) (Loo *et al*., 2018; Subashini *et al*., 2014).

Gold Nanoparticles (Au NPs) have a unique characteristic of photosensitive plus electrical properties, but these are mostly dependent on shape and size, therefore they gained attention of scientific society (Verissimo *et al*., 2016). There is no evidence of Au NPs as antibacterial all have antifungal properties, Au NPs when combined with some antibiotics or other drugs their antibacterial or antiviral activity is improved comparing it to single antibiotic or other drug (Y. Zhang *et al*., 2015).

Different studies suggested that neither functional activity nor bacterial growth is affected by Au NPs, but when they are conjugated with antibiotics have a negative effect on growth of bacterial cell (Burygin *et al*., 2009). There is great importance of Au NPs which act as vehicles for the delivery of antibiotic and bactericidal effect of antibiotics is enhanced (Y. Zhang *et al*., 2015).

Zinc Oxide nanoparticles (ZnO NPs) have a wide spectrum of activity against bacteria according to research it is an antimicrobial agent against spoilage and pathogenic microbes (Duffy *et al*., 2018; Tony Jin & He, 2011; Raghupathi *et al*., 2011; Ren *et al*., 2012; Savi *et al*., 2013; Xie *et al*., 2011). At high concentration of 0.24mg/ml they may inhibit the growth of different microorganisms like strain of *E. coli 0157:H7*, *Salmonella enterica*, *Listeria monocytogenes*, *Serovar enteritidis* (T. Jin *et al*., 2009; Y. Liu *et al*., 2009), and there are some other inhibition reports against, *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus subtilis*, *Staphylococcus epidermidis* and *Streptococcus pyogenes* (Jones *et al*., 2007). The size of ZnO NPs have a direct relation with their activity like ZnO NPs activity increases when the size is reduced (Agarwal & Nair, 2013), by permeating into the cell membrane the growth of microorganism is inhibited (Siddiqi, ur Rahman, *et al*., 2018). Different oxidative stresses harms protein, lipids, carbohydrates, and DNA (Siddiqi, Husen, *et al*., 2018). Oxidative stress mechanism supports that cellular function is disrupted by lipid peroxidation (Rikans & Hornbrook, 1997), as a result cell membrane blebbing, irregular cell surface and increase the permeability of membrane. When treated with ZnO NPs (Siddiqi, ur Rahman, *et al*., 2018), the cells of E. coli O157:H7 (Kelly *et al*., 1998) were prompted the leakage of membrane observed by transmission electron microscopy and Roman Spectroscopy.

Titanium dioxide (TiO*2*) has a photo dependent antimicrobial activity (X. Jiang *et al*., 2010; P. Liu *et al*., 2010; Wu *et al*., 2010) and has a free radicle production quality. By causing peroxidation these free radicles affect phospholipid bilayer, peptidoglycan, and bacterial lipopolysaccharide (LPS) (Shaikh *et al*., 2019). Nitric oxide (NO) is a highly reactive, short half-life and lipophilic nature can pass to cell wall (Shaikh *et al*., 2019). The specificity effect of NO is dependent upon the nature of nanoparticles at target site and at high-rate concentration gradient are produced (Weller, 2009). Although NO releasing silica nanoparticles are being used against *P. aeruginosa* as novel antimicrobial and have adverse effect on infection wounds of Acinetobacter baumannii by releasing nitric oxide nanoparticles practice results collagen degradation, suppurative inflammation and reduce the microbial burden (Shaikh *et al*., 2019). Copper nanoparticles (Cu NPs) direct contact to the bacterial cell increase their ability to prevent the growth of bacteria (Sánchez-López *et al*., 2020). Cu nanoparticles mode of action is not clear yet, but a concept that due to electrostatic interaction the NPs adhere to cell wall. Separation of Cu^{2+} prompts the reactive oxygen species (ROS) generation to have an interaction with cellular membranes. Cause membrane damage because ions have capability to enter the cell and results bacterial cell leakage and the cell is disrupted (Lara *et al*., 2010; Slavin *et al*., 2017). Cu nanoparticles antimicrobial activity have been studied against some microorganisms for example, *Escherichia coli*, *Vibrio cholera*, *P. aeruginosa*, *Salmonella typhus*, S. *aureus*, *E. faecalis*, *B. subtilis* and *S. faecalis* (Rajendran *et al*., 2017). Magnesium oxide (MgO) nanoparticles have antibacterial activity specifically against *E. coli*. Although, NPs antimicrobial activities are dissimilar to membrane lipid peroxidation because of oxidative stress. Different studies indicated that cell membrane is damaged in MgO nanoparticles when they attach to membrane, magnesium ions are release, change in pH and ultraviolet illumination. Just limited quantities of intracellular ROS are available; MgO NPs treatment doesn't fundamentally alter the levels of phosphatidylethanolamine or lipopolysaccharide (LPS) in cell barriers, showing MgO NPs don't prompt lipid peroxidation. Moreover, levels of ROS-related intracellular proteins don't change, yet a few significant metabolic cycles related with proteins engaged with amino acid, starch, and nucleotide digestion are especially diminished (Leung *et al*., 2014).

Lipid nanoparticles (LNPs) have a specific delivery system is known as promising drug delivery system (DDSs). Lipid-based drug delivery systems are unusually multipurpose that have ability to transport the hydrophilic and hydrophobic molecule so (Markowska *et al*., 2013). Liposomal bacteriocin formulations helped to fight a series of L. monocytogenes epidemics in the late 1990s and 2000s (Benech *et al*., 2002; Degnan *et al*., 1993; Were *et al*., 2004). Bactericidal peptides are ribosomal synthesized bacteriocins. This combination was studied against different food industrial microbes which are responsible of

contamination results that this combination if effective for food-borne pathogens in both group of bacteria Gram-positive as well as Gram negative. Liposome bacteriocins are specifically used against the *L. monocytogenes* that contaminate food. *Streptococci's* community produces insoluble glucan which is responsible for dental caries that is a common type of biofilms. By increasing the concentration of nisin-loaded liposomes decrease the glucan synthesis. Furthermore, the presence of lipid phytosphingosine cation in the liposomal formation increases the action of ant cariogenic (Yamakami *et al*., 2013). Selenium has a great importance in a biological system function as nutrient and integrated with antibacterial agent. Selenium is required for the growth and health maintenance is used in diet as a trace element (Skalickova *et al*., 2017). Selenium nanoparticles (Se NPs) have ability to exhibit antioxidant (Forootanfar *et al*., 2014), anticancer (B. Yu *et al*., 2012), antibacterial (Shakibaie *et al*., 2015) and as well as anti-biofilm properties according to recent studies. Their antimicrobial activity against bacteria, fungi, and yeasts (Beheshti *et al*., 2013; Shahverdi *et al*., 2007). Selenium NPs prevent bacterial progression at protein's low concentration (Vahdati, M Reports, 2020). Another significant element of this mixture nano framework is that lysozyme has likewise assumed a fundamental function in antibacterial property of SeNPs. Though singular Lysozyme ($100\ \mu gmL^{-1}$) isn't amazingly discovered successfully on hindrance of S. aureus, its essence in the Nanohybrid framework containing $1\ \mu g.\ mL^{-1}$ SeNPs has introduced ideal synergistic impact and 100% restraint; while the nanoparticle itself has not initiated such impact at this fixation (Vahdati & Tohidi Moghadam, 2020).

Graphene oxide (GO) is a selective antimicrobial agent and has a broad-spectrum which depends upon photothermal therapy. In photo-thermal therapy, photo sanitizer (PS), oxygen, and light sources are involved in the treatment of cancer (Castano *et al*., 2006; W. Fan *et al*., 2016) as well as to kill microbes of infectious diseases (Wainwright *et al*., 2017). In photothermal therapy, the PS and oxygen produce Reactive Oxygen Species (ROS), hydroxyl radicle (OH), singlet oxygen (O_2), and superoxide radical (O^{2-}) which involved in cell damage. Their effects are local because of their short lifetime and reactivity of ROS (Dolmans *et al*., 2003; Lan *et al*., 2019).

Table 3: Mechanism of Action of NPs against pathogens

Strength And Limitation of The Nanoparticles: It has been thoroughly examined that how antibiotics resistant is a new challenge in today's world and the use of nanoparticles to overcome this huge problem. Drug resistant bacteria development is increasing rapidly, especially in nosocomial strains, and as a result it has become one of the prime issues of the health problems in the world. And it's expected that this number may increase in the future.

However, the inhibitory effects of metal oxide nanoparticles have been validated equally against resistant bacteria and antibiotic-sensitive bacteria. Most importantly, since the nanoparticles are able that they can attack the different bacterial cell components that lies inside the cell, therefore, the bacteria are thought to be unable to create resistance against nanoparticles. This is the main feature that they are becoming a superior alternative to recent antibiotics therapy. Nevertheless, the biggest fault that inhibits the clinical application of the nanoparticles is the generation of toxicity which is the biggest disadvantage. On the contrary, day by day regarding Nanotechnological advances number of studies are being held for more and more improvements. The use of metal oxides for different skin infection treatments as a clinical point of view are considered (Allahverdiyev *et al*., 2011).

Using cell culture, the biocompatibility of the nanoparticles can be measured by the help of in vitro analysis. And moreover, through in vivo models their possible effects must be measured such as their toxicity, clearance, and metabolism for the purpose that they enter the body through different routes such as ingestion, skin contact, inhalation, and intravenous and oral injection (Beyth *et al*., 2015). Studies has also indicated another issue which is the accumulation of the intravenously injected nanoparticles in the lung, colon, bone marrow, and spleen etc. (Hagens *et al*., 2007). Other side effects of the nanoparticles include hepatotoxicity and nephrotoxicity due to the production of the free radical-mediated oxidative stress by the interaction of antimicrobial nanoparticles with cell components and result in cytotoxicity in several organs (De Jong & Borm, 2008). Interestingly, according to recent research resistance has been developed against silver nanoparticles by *E. coli* and *P. aeruginosa*. The main cause of resistance is the formation of flagellum that prevents the attachment of NPs to the cell. Whereas resistance can be reduced using flagellin inhibitors (Panáček *et al*., 2018).

CONCLUSIONS

This review provides a comprehensive study of NPs and their synergistic role with various antibiotics. In addition to their mechanism of action against various pathogens along with the biosynthesis of different nanoparticles. The effects of current and next-generation antibiotics could be enhanced to combat resistant bacteria. New drugs and different therapeutics for treatment could also be discovered via he further study of nanoparticles and its diverse effects such as synergy.

Table 1: Nanoparticles Classification & Characterizations Adopted from (Bhatia & Bhatia, 2016; Mabena *et al*., 2011; Saeed & Khan, 2016)

Types of Nanoparticles	Size (nm)	Features	Functions
Carbon-based NPs	0.5–3 diameter and 20–1000 length	Discover in 1985, cylindrical shape of carbon sheets, layers can be SWNT or MWNT. These have gorgeous energy and are good conductors and insulators.	Gene silencing, diagnostics, Reduced toxicity, transport genes, peptides, and drugs.
Ceramic-based NPs	<50 nm	They are built by oxides, carbides, like calcium, silicon, and so on. Found in the fluid, polycrystalline, hole-like. Superb carriers for drugs and genes	high warmth resistance, used in chemical & biomedical fields (carriers for drugs, genes, proteins, imaging agents)
Metallic NPs	<100	produced from metals through chemical, electrochemical, and photo-chemical approaches. AgNPs used in chemotherapy, radiosensitizers, diagnosis, carrier	Transports drug, gene, to the Target site, Diagnosis, boosts radiotherapy.
Semiconductor NPs	2–9.5	Semiconductor belongs to group 3-4, 5, 6, 2-3-6, elements of the periodic table Luminescence, and excessive photostability	DNA hybridization, probe to label organs and tissues, Immunoassay, Cancer Therapy
Polymer NPs	10–1000	Decomposable, biocompatible, cover, or protect the whole drug.	Outstanding transporter of drugs. Made up of natural and artificial polymers. Control of drug discharge.
Lipid-based NPs	50–100	**Are spherical contains Surfactants or emulsifiers. Biocompatibility, decomposable, less hazardous, and flexible.**	Transport gene, protein, Drugs, etc.
Magnetic NPs	less than 100nm	**Characterization based on sensitivity, diagnosis, and antimicrobial activity.**	Cancer therapy, Magnetic resonance imaging (MRI), Identification of targeted orang and tissue.

Table 2: Synthesis of Natural Products from Precursors in Specific Samples

Precursor	Sample	NPs Creation				NPs Synthesized	References
		Bacteria	Fungi	Algae	Plants		
$AgNO_3$	Feces	*E. coli* TCC 8739				Ag	(Müller et al., 2016)
	Tiger nut	*K.pneumoniae* UVHC5				Ag	(Müller et al., 2016)
	Carrot Juice	P.jessinii				Ag	(Müller et al., 2016)
	Soil samples from Cochin	*Bacillus* strain CS 11				Ag	(X. F. Zhang et al., 2016)
	Healthy coral samples	*Alcaligenes* strain MGL-D10				Ag	(Anandalakshmi et al., 2016)

	Leaf of Garcinia xanthochymus	*Becillus cereus*				Ag	(Gahlawat et al., 2016)
		Actinobacteria *Rhodococcus* NCIM 2891				Ag	(Chanlett, 1947; Otari et al., 2014)
	Silver mine	*Pseudomonas stutzeri* AG259				Ag	(Klaus et al., 1999)
		Cornebacterium sp. SH09				Ag	(Hulkoti & Taranath, 2014)
	Mandapam coastal region				*Gelidiella acerosa*	Ag	(Vivek et al., 2011)
	Coastal Saltmarsh Plant				*S. portulacastrum*	Ag	(Nabikhan et al., 2010)
					Avicennia marina mangrove plant	Ag	(Gnanadesigan et al., 2012)
	Marine *seaweed*			Seaweed *S. wightii*		Ag	(Govindaraju et al., 2009; Kamat et al., 1998)
$HAuCl_4$	Seaweeds marine alga			*S. wightii*		Au	(Singaravelu et al., 2007)
Carboxylate	Submerged Marine Rocks			*Ulva fasciata*		Ag	(Rajesh et al., 2012)
	Taxus plan		fungus *Verticillium*			Ag	(Mukherjee et al., 2001)
	Soil		*Fusarium oxysporum*			Ag	(Durán et al., 2005)
$HAuCL_4$			*Y. lipolytica* NCIM 3589			Au	(Agnihotri et al., 2009; Jain et al., 2004)
$SbCl_3$			*Saccharomyces cerevisiae*			Sb2O3	(Jha et al., 2009)
	Indian Ocean		*Rhodosporidium diobovatum*			PbS	(Seshadri et al., 2011)
Palladium			*Saccharomyces cerevisiae*			Pd	(Sriramulu & Sumathi, 2018)

$AgNO_3$			*Yarrowia lipolytica* NCYC 789			Ag	(Apte et al., 2013)
$HAuCl_4$			*Y. lipolytica* NCIM 3589			Au	(Agnihotri et al., 2009; Jain et al., 2004)
Chalcogen-oxyanion	Industrial waste	*Ochrobactrum* strain MPV1				SeO_3^{2} & TeO_3^{2}	(Zonaro et al., 2017)
$BaSO_4$		immobilized *Rhodobacter sphaeroides*				CdS	(H. Bai et al., 2009; H. J. Bai et al., 2006)

Table 3: Mechanism of Action of NPs against pathogens

Nanoparticles	**Effect**	**Target Bacteria**	**Mode of Action**	**References**
Ag NPs	Bactericidal	*E. coli* *S. typhi* *B. subtilis* *MRCNS* *ESBL-positive* *S. aureus* *K. pneumonia* *Staphylococci* *MRSA* *Vibrio cholera*	Metabolic processes are disrupted when they are interacting with different enzymes of disulfide group, release of iron, loss of respiration, permeability as well as cell wall division, cell wall lysis by Ag NPs ampicillin, stops unwinding of DNA, DNA loses their ability of replication.	(Sriramulu & Sumathi, 2018; Stylianopoulos & Jain, 2015)
Au NPs	Bactericidal & Bacteriostatic	*E. faecium* *E. coli* *P. aeruginosa* *E. cloacae*	Membrane potential is change which decreases the ATPs level and also the binding of tRNA is inhibited to ribosome.	(Thota et al., 2017; Todar, 2011)
TiO_2 NPs	Bactericidal	*L.monocytogenes* *E. coli 0157:H7* *S. enteritidis* *P. fluorescens* *S. aureus*	Loss of respiration ability All bacteria are killed approximately, and these are toxic under the ultra-violation radiation. Generation of ROS Membrane fluidity and cell disruption is enhanced by the lipid peroxidation. TiO2 photo activation stimulates bactericidal effect as well as peroxidation of membrane phospholipids	(Vahdati, M Reports, 2020; Van Hoek et al., 2011)
ZnO NPs	Bactericidal & Bacteriostatic	*B. subtilis* *L.monocytogenes* *E. coli 0157:H7* *P. fluorescens* *S. enteritidis* *S. typhimurium* *S. aureus*	In the presence of ZnO nanoparticles the morphological changes occur like • Membrane permeability increases • Enzyme inhibited. • Electrostatic interaction • ROS generate to particle surfaces. • Zink ions are released.	(Cuenca et al., 2006; David L. Cohn, 1997; Siddiqi, ur Rahman, et al., 2018)

			• Membrane dysfunction • Due to nanoparticles internalizing to the cell	
CuO NPs	Bacteriostatic	*E. coli* *B. subtilis* *S. aureus* *L.monocytogenes*	It damages the vital enzymes of bacterial cell when inter to the cell via cell membrane, and also damages the nucleic acid when penetrated to the cell wall	(J. Blaser, 2016; Vivek et al., 2011)
MgO NPs	Bactericidal	*B. subtilis* *S. aureus* *E. coli* *B. megaterium*	Damages the cell membrane which causes bacterial cell death due to leakage of intracellular contents	(Tu & Fang, 2016; Wainwright et al., 2017)
CaO NPs	Bactericidal	*S. aureus* *S. epidermidis* *E. coli* *S. mutans*	Damages the cell membrane which causes bacterial cell death due to leakage of intracellular contents	(Wang et al., 2017; Weller, 2009)
Al_2O_3 NPs	Bactericidal	*P. aeruginosa,* *B. subtilis* *K. aerogenes* *E. coli* *P.desmolyticums* *S. aureus*	Damages the cell membrane which causes bacterial cell death due to leakage of intracellular contents	(Ansari et al., 2015)
Graphene Oxide NPs	Bacteriostatic	*Klebseilla* *Staphylococus* *Bacillus subtilis* *Staphylococus* *Pseudomonas aeruginosa* *Enterobacter aerogenes*	Disrupt the bacterial cell by bind with the LPS, prevents the nutrient uptake Create oxidative stress and physical disruption but the cell remains alive.	(Castano et al., 2006; Dolmans et al., 2003)
Se NPs	Bacteriostatic	*S. aureus*	Inhibition of DNA, RNA, Protein and growth, Causes alteration in Non-coding RNA genes.	(Vahdati, M Reports, 2020)

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