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Review Article

Sustainable Antimicrobial Nanomaterials: A Promising Treatment for Multiple Drug Resistant Microorganisms

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ABSTRACT

Antibacterial drugs had an essential role in the treatment of various diseases from a long-time whereas excess use leads to resistance and toxicity which is a great challenge in the health sector. The most important factors responsible for the spread of antibiotic resistance includes globalization, self-medication, repetitive and excess use of antimicrobials, continuous intake of broad-spectrum agents, and less availability of an effective antimicrobial agents. The increased resistance of antibiotic towards many microorganisms threatens further use in the treatment or the increased dose may lead to toxicity. It is also estimated and found that if no new antibiotics or antibacterial drugs discovered in the current situation then there is an urgent need to identify and develop an alternative effective method for the treatment of antibiotic resistant. Green synthesized nanoparticles are most effective, eco-friendly, and efficient on resistant microorganisms. Therefore, the present review is to summarise the mechanisms, classifications, limitations, and applications, of various nanotherapeutics nano formulations as a promising and effective treatment for the repetitive development of antibiotic resistance by different strains of bacteria.

Keywords: Nanomaterial, Antibiotic resistant, Microorganism, Metal, Antibacterial, Chemotherapy.

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INTRODUCTION

Bacterial adhesion and growth in daily life is a critical worry that causes considerable harm in a number of pharmaceutical, textile, water treatment, marine transportation, and food packaging industries.[1] A significant issue and challenge for public health is the growth of pathogenic species resistance to antibiotics and diseases brought on by Multidrug-Resistance (MDR) bacteria. Additionally, nanomaterials demonstrate promising methods by defining novel tactics for limiting bacterial activity, which is a critical requirement in the current environment.[1] The emergence of antibiotic resistance in recent decades has made it one of the top issues for hospital infection control services.[2] The World Health Organization recently classified and published the list of some pathogenic microorganism specifically bacteria as an important pathogens for which new antibiotic or novel formulations needed to be synthesis and develop.[3] The evolution of drugs and medicine, as well as changes in human lifestyle, may be biological reasons for the development of resistance in the human body. As a result, an influential treatment for antibiotic-resistance microorganisms is needed. Antibiotics are used to prevent infection in various areas including treatment of immunocompromised patients, patient undergone surgery or taking chemotherapy.[4] The majority of current infectious diseases are incurable due to the severity and persistence of infections caused by microorganism biofilm formation.[5,6] The evolutionary process behind resistance, on the other hand, must reveal the genetic causes as well as the physiological consequences of its acquisition.[7,8]

Hospital and some community-based data showed an increase in the burden of antimicrobial resistance. This makes it imperative to search for alternative treatments. Biological synthesis of nanoparticles was observed to be a less energy utilizing single step bio-reduction method, using eco-friendly resources such as plant extracts, bacteria, fungi and micro algae. The green synthesis of nanoparticles using plant material is of potential applications and combinatorial approach of green synthesized nanoparticles with antibiotics may prevent microbial drug resistance and improve an efficacy of antibiotic in resistant microbes. Thus, the present review is planned to project the green synthesized nanoparticles with biologically active metals, and its combination with antibiotics and antibiotic nanoparticles as a promising alternative for management of MDR conditions and deaths.

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Antibiotic Resistance

A microorganism's insensitivity or resistance to antimicrobial medicines (structurally irrelevant and different molecular targets) whereas previously sensitive to same antibiotics is known as Multidrug Resistance (MDR).[9,10] The classification of resistance has been demonstrated in (Figure 1). As per World Health Organization (WHO), the resistant microorganisms (such as bacteria, fungi, virus, and parasites) can withstand antibacterial, antifungal and antiviral drugs action, result in ineffective treatments and continues the spread of infection. Superbugs are capable infecting agents such as bacteria, fungi, viruses, and parasites that have high degree of MDR with increased mortality and morbidity. In the modern era, as these deadly diseases such as Cancer, Tuberculosis, Pneumonia, HIV, Influenza, Malaria, Yeast infections, and many others are major causes of death, with this indicating MDR is also a global threat to public health for coming generations. Antimicrobial Resistance (AMR) or MDR is the reason why microbes fail to respond to standard drugs, thereby increasing the duration of the course of treatment and worsening the situation of people who cannot afford such expenses.[7] Use of multiple broad-spectrum agents, and lack of good antimicrobial stewardship can be listed as the factors most responsible for the spread of antibiotic resistance species.[8]

Resistance by ionizing radiations

Although ionising radiations such as UV and IR damage nucleic acid, protein, and other cellular materials in microorganisms, it has been discovered that microorganisms have developed radiation resistance. The majority of the literature reported that this radio resistance is specifically based on an experiment related to acute irradiation in pure culture developed under normal growth conditions. This type of resistance evolved in organisms whose natural environment requires them to survive in UV radiation, desiccation, toxic chemicals produced by competitors or hosts like severe oxidative and genotoxic stresses.[11] Concurrent with the rise in antibiotic-resistance bacteria, researchers are turning to alternative therapies such as traditional plant-based medicines, bacteriophage therapies, and combinational therapies.[9] Biologically synthesised metallic nanoparticles are gaining popularity for a variety of applications because they are nontoxic and environmentally friendly. Table 1 summarises the resistance microorganisms, as well as their resistance mechanism and activity.

ROLE OF NANOMATERIAL'S AGAINST MDR MICROORGANISMS

The management of antibiotic-resistance bacteria, nanotechnology plays a significant role. Nanoparticles, nano diamonds, Nano crystals, 2D nanomaterial's, nanotubes, nanofibers, nanovesicles, nanosheet or hydrogel nanonetworks quantum dots have all been reported as effective drug delivery and treatment. The focus of this review will be on the utilisation of biologically active metals, metal ions, metal ion complexes with antibiotics, green produced nanoparticles, and the combinatorial effect of diverse nanoparticles for the treatment of MDR microorganism-based disorders.[23,43] Nanomaterials exhibited some physical properties such as a large number of the surface atom, large surface energy, reduces imperfections and spatial confinement, optical, magnetic, and mechanical.[43]

Nanoparticles are synthesized in a variety of shapes (spherical, prismatic, rod, tube, fibre, etc.,) structure (amorphous, monocrystalline, polycrystalline), dispersity (monodispersed, polydisperse, etc.,) and classified into 0D, 1D, 2D, and 3D,[44] and the shape affect the biological activity of the NPS. Moreover, the biological activity is also gets affected by the size of the nano-particles. The decrease of the size of nanoparticles increases their surface-to-volume ratio which thereby enhances their reactivity.[45]

ROLE OF METAL IONS IN THE TREATMENT OF RESISTANCE MICROORGANISMS

As reported by the scientist, the silver ions exhibit an oligodynamic effect only in dissolved ionized form. Moreover, the German scientist reported that the silver ion exhibits the highest bactericidal effect than gold and copper. Moreover, silver also played a catalyst role in the oxidation of bacterial protoplasm and its destruction by oxygen dissolved in water. Silver ions act indirectly by increasing the free radicles in the cells which reduces the intracellular active compounds of oxygen. It is also hypothesized that the silver ion gives an antimicrobial effect by inhibiting the transport of Ca^{+} and Na^{+}[44].

ROLE OF NANOPARTICLES (NPS) IN ANTIMICROBIAL RESISTANCE

Nanoparticles (1-100 nm) have shown broad antibacterial activity against Gram-positive and Gram-negative bacteria. Zinc nanoparticles have activity against *staphylococcus aureus* whereas silver nanoparticles had concentration-dependent antibacterial activity against *Pseudomonas aeruginosa* and *Escherichia coli*. Nanoparticles interacts with bacteria by different mechanisms like interacting with bacterial cell wall, DNA, enzyme, ribosomes, lysosomes, causing oxidative stress, enzyme inhibition, protein deactivation, cytoplasmic variation in membrane permeability, gene expression levels and electrolyte balance.[44,45] The multiple and simultaneous mechanisms of nanoparticles, as shown in Figure 2, would necessitate gene mutations in a microbial cell for antibacterial resistance. As a result, nanoparticles interact with bacterial cell walls directly and are less likely to promote resistance in bacteria.[47]

NPs that are metallic or organic and functionalized by target drug delivery have been reported to improvise and synergize

Table 1: Microorganisms, Resistance Towards Antibiotics and Microbial Activity.

Sl. No.	Microbial Strains	Resistance to Antibiotics	Resistance Mechanism	Microbes Activity	References
1.	*Staphylococcus aureus* Gram-positive ubiquitous strain	Penicillin, Methicillin, Vancomycin (VAM), Daptomycin (DAP)	Acquired a plasmid-encoded beta-lactamase that conferred resistance to penicillin. Vancomycin-intermediate *S. aureus* (VISA), Heterogeneous VISA (hVISA), and high-level Vancomycin-Resistance *S. aureus* (VRSA). DAP is bactericidal against MRSA and VISA strains and was used to treat skin/soft-tissue infections.	Apart from causing infections in cutaneous lesions can result in severe cases of pneumonia, meningitis, endocarditis, septicemia, and even systemic infections, with risk of death. MRSA usually has more severe clinical manifestations and is difficult to treat, as methicillin resistance indirectly affects other virulence factors and enhances the pathogenesis of bacterium. The *in vivo* development of VISA and hVISA has led to treatment failures and prolonged hospitalization.	10-14
2.	*Streptococcus pneumonia*	Penicillin	Amino acid substitutions in the proteins encoded by pbp1a, pbp2b, and pbp2x, especially in their transpeptidase domains, are the primary causes of Penicillin Resistance (PC-R).	Causes bacterial infections such as pneumonia, otitis media, occult bacteramia, and meningitis.	15
3.	*Enterococci* *Enterococcus faecium,* *Enterococcus faecalis*	Vancomycin Linezolid	G2576T mutation in the 23S rRNA gene. Mutations in the L3 and L4 ribosomal proteins as well as two plasmid-borne genes (CFR and Optra).	A common cause of nosocomial infections and has also been associated with urinary tract infections, hospital-acquired bloodstream infections, endocarditis, abdominal and pelvic abscesses, and chronic periodontitis.	12-18
4.	*Enterobacteria* *Klebsiella pneumoniae*	Carbapenem Cephalospors	To overexpression of amps, and ESBL associated with loss or modifications of porins. However, later they were confirmed to produce a new type of enzymes (carbapenem's) with the capacity to inactivate any type of beta-lactam, including the carbapenems.	Pneumonia, Urinary Tract Infections (UTIs), bloodstream infections and sepsis.	19

Sl. No.	Microbial Strains	Resistance to Antibiotics	Resistance Mechanism	Microbes Activity	References
5.	*Acinetobacter baumannii* Gram-negative, aerobic coccobacillus	Carbapenem	Intrinsic or acquired Resistance, mediated by several factors, such as loss of membrane permeability and the production of betalactamases (cause of bacterial resistance), enzymes that degrade betalactam antibiotics. Resistance by combining different mechanisms such as a change in the affinity to PBPs and efflux pumps. However, the main forms of resistance to carbapenems are the expression of carbapenemases of group B and D of Ambler, Metallo-b-lactamases, and OXA respectively.	Risk factors for infection and colonization by MDR *A. baumannii* include prolonged hospitalization.	20,21
6.	*Pseudomonas aeruginosa* Nonfermenting gram-negative bacillus	Carbapenems	Due to the low cell wall permeability of this microorganism, which restricts the uptake of antibiotics, associated with wide resistance mechanisms, such as efflux pumps and enzymes, which modify or degrade antibiotics and drug targets? The main carbapenemases expressed by *P. aeruginosa* are from class B of Ambler, called Metallo-ß-lactamases (IMP, VIM, SPM, GIM, NDM, and SIM families). These enzymes confer resistance to carbapenems and are encoded in plasmids and integrons of class 1, which are responsible for their rapid global spread by horizontal transfer.	Responsible for nosocomial infections, it is one of the most important opportunistic pathogen causing bloodstream infection, Urinary tract infection, and ventilator-associated pneumonia, especially in critically ill patients receiving intensive care.	22-24
7.	*Escherichia coli*	Ampicillin, Piperacillin, Cefalothin, Cefuroxime, Sulfamethoxazole/ Trimethoprim, Tetracycline	The Cephalosporin group may be resistance to either the decreased affinity of existing PBP (penicillin-binding protein) components or maybe insensitive PBP. Trimethoprim can be resistance against *E. coli* by 3 different mechanisms: changes in cell permeability, loss of drug binding capacity and alteration in dihydrofolate reductase.	Traveler diarrhea, Urinary Tract Infection (UTI) is common apart from this they also caused meningitis, and sepsis sometimes leads to death.	25,26
8.	*Neisseria gonorrhoeae*	Cephalospors	Cephalosporine group can be resistance by two mechanisms either decreased affinity of existing PBP or insensitive PBP.	It causes gonorrhea which is a Sexually Transmitted Disease (STD).	27-29

Sl. No.	Microbial Strains	Resistance to Antibiotics	Resistance Mechanism	Microbes Activity	References
9.	*Mycobacterium tuberculosis*	Rifampicin, isoniazid, and fluoroquinolone	Mutation in the rpoB gene that codes for the β subunit of the RNA polymerase. This leads to conformational changes occurs that decrease the affinity for the drug and result in the development of resistance.	May cause both pulmonary tuberculosis and Extrapulmonary Tuberculosis (EPTB) like ocular TB, skeletal TB, etc.	30-32
10.	*Candida*	Fluconazole Echinocandin	Azole class resistance towards candida by 4 different mechanisms: low the binding affinity of lanosterol 14-α-demethylase for drug, or upregulation of drug transporters or by increasing the lanosterol 14-α-demethylase or by inactivation of C5 sterol desaturase leading to alteration in the ergosterol synthetic pathway. Resistance occurs by decreased glucan synthase processivity for the drug.	It causes oral and vaginal candidiasis vulvovaginal candidiasis.	33-35
11.	*Aspergillus*	Azoles	Due to the long duration of the drug or increase number of reproducing microorganisms. Apart from these there are changes in codon 220 also observed.	It causes allergic syndromes, non-invasive infection, and also invasive aspergillosis.	36-37
12.	*Herpes simplex virus* (HSV)	Acyclovir, Famciclovir, Valacyclovir	Long-term medication leads to drug resistance. The mechanism which may be responsible for drug resistance are: decreased production of viral TK, or complete deficiency in viral TK activity, and another one is viral TK protein and DNA polymerase with altered substrate specify.		38
13.	Human Immunodeficiency Virus (HIV)	Antiretroviral drugs	Resistance occurs by: mutation in co-receptors used by HIV to establish infection.	Acquired Immunodeficiency Syndrome (AIDs).	39,40
14.	Hepatitis B virus (HBV)	Lamivudine	Mutation in the reverse transcriptase domains of the viral polymerase gene leads to drug resistance and another mechanism is the interaction between HBV polymerase and drug, which interferes with the inhibitory effect of the drug on the viral polymerase.	It causes cirrhosis, hepatocellular carcinoma.	41,42

the bactericidal action of antibiotics when combined with other antimicrobial agents.[48,49]

The triple mechanism of action includes oxidative stress, non-oxidative stress and metal ion release, as well as the combination with other antimicrobial agents with NPs, can prevents microbe resistance.[50] Niemirowicz *et al.*[51] investigated the effects of core-shell metallic NPs in combination with cathelicidine LL-37, synthetic ceragenins such as CSA-13 and CSA-131, and traditional antibiotics against MRSA and reported synergistic activity. According to the findings, MNPs also increase the efficacy of these antimicrobial drugs. As reported in the literature, the MICs of erythromycin, ciprofloxacin, VAM, and methicillin were reported to be effectively reduced when metal oxide NPs were combined with them. Photoinactivation of resistant strains of *K. pneumoniae* and *E. coli* by monomeric methylene blue conjugated gold NPs was examined where MDR bacteria were killed at a rate of 97 percent.[52,53]Authors suggested that this NP-based photodynamic therapy might be used as a possible treatment for MDR infections. Furthermore, the trimethyl chitosan-capped Ag NPs were found to exhibit strong antibacterial activity against resistant *A. Baumannii*, with a MIC of £12.25 mg/mL. As a result, NPs appear to be a promising approach for combating bacterial MDR.[2]

Graphene Oxide (GO) 2D nanomaterial exhibited unique properties and applications in biomedicals, according to Han *et al.* 2020. Graphene oxide was functionalized with the hydrophilic nature polymers and used as a carrier for silver nanoparticles and drug Sulfadiazine (SD), as shown in (Figure 3). SD is a broad-spectrum antimicrobial agent, whereas loading Ag NPs on GO results in synergistic antibacterial activity. In comparison to a system lacking SD, the 2D nanoparticle was a novel antibacterial hybrid system with three times the antibacterial activity due to triple synergy such as bacterial capping effect of GO, puncture effect of Ag NPs, and inhibition effect of SD. This novel hybrid antibacterial system prepared by simple, rapid, microwave assisted green process discovered good antibacterial activity with 0.78 μg/mL MIC which is very low, improved efficiency and faster sterilization.[54]

NANOMATERIAL'S IN CANCER THERAPY

Nanomedicines such as nanodrugs, nanoparticles, nanodevices, and nanocarriers can help with issues such as treatment of resistant microorganisms, narrow therapeutic effect, and unwanted harmful effects of existing anticancer medications, as well as their limitations. Nano systems used for detection, diagnosis, and treatment include metallic nanoparticles, liposomes, carbon rods, carbon nanotubes, quantum dots, polymeric micelles, and dendrimer. A non-biodegradable nanoparticle accumulates in the tissues and causes harm. MDR is a major impediment to cancer treatment that causes chemotherapies to fail in a variety of cancers, including breast, ovarian, lung, gastrointestinal, and haematological malignancies. MDR is a major problem to cancer treatment due to which chemotherapies fails in a variety of cancers, including breast, lung, ovarian, haematological and gastrointestinal malignancies. Furthermore, the therapeutic efficacy of anticancer medicines or nanoparticles has been questioned.[55,56]

Gurunathan *et al.*[57] conducted a review to summarise and analyse current advances in the field of combination therapy using NPs and anticancer medicines. The highlights of the review were the study of carbon NPs, Liposomes, polymeric micelles, polymeric NPs, dendrimers, fullerenes, nanodiamond, Carbon Nanotubes (CNTs), Graphene Oxide (GO), GO nanocomposites, and metallic NPs. Nanotechnology has proven to be an effective technique in combination therapy. However, significant advances in nanotechnology are required for clinical translation.

Targeting theranostic agents in the development of cancer treatment therapeutic is a complex and fascinating research topic. Theranostic metallic nanoparticles, or TMNPs, have been demonstrated to be a novel and effective treatment for theranostic applications imaging, diagnostics, and therapeutic delivery of active chemicals to tumor-specific cells. TMNPs have been used in magnetic resonance imaging as well as a colloidal mediator for cancer magnetic hyperthermia, implying that they can aid in diagnosis and treatment. The multimodal theranostic elements of MNPs, such as active and passive targeting (HER2, Folate, Angiogenesis, and so on), as well as the RES escape route, demonstrate the importance of Multifunctional Metallic Nanoparticles (MNPs) in oncology.[58]

METHODS FOR SYNTHESIS OF NANOMATERIALS

Nanoparticles are created using both bottom-up and top-down methods (Figure 4). Bottom-up synthesis is analogous to denovo nucleotide synthesis, in which nucleic acid blocks are constructed from starting material, like how particles are constructed from molecular assembly of atoms and molecules. Biological and chemical methods include sol-gel processing,[25] chemical vapour deposition,[26,59] flame or plasma spraying synthesis,[60] laser pyrolysis, atomic or molecular condensation, electrodeposition, chemical solution deposition, Langmuir Blodgett method, soft chemical method, catalytic route, hydrolysis,[61] co-precipitation method, and wet chemical method.[28-30] A top-down method is also used to fragment bulk material into nanoscale stuff. Laser ablation, vacuum vapour deposition,[62] plasma arcing, spray pyrolysis, thermal evaporate, ultrathin films, sputter deposition, lithographic techniques, layer by layer growth, molecular beam epistaxis, and diffusion flame synthesis of nanoparticles,[63] and only rarely a chemical procedure such as Sono-chemical method.[64] Researchers are now shining a light on the environmental friendly approaches to synthesis represented by nano biosynthesis.[65]

The drawback of physical and chemical methods of producing NPs, such as intense radiation and concentrated reductant as well as stabilising chemicals that are harmful to the environment and human health. In the biological synthesis of nanoparticles from bacteria, fungi, plant extracts, microalgae and enzymes are uses, a single-step bio-reduction method[66] and eco-friendly resources.

GREEN METHODS IN NANO SYNTHESIS A BIOLOGICAL APPROACH

When metal ions, metal salts, and many other compounds come into contact with biological systems, they are converted into less toxic forms, allowing organisms to be used in the production of Nanoparticles (NPs).[67] Plants, algae, fungi (including yeast and actinomycetes), bacteria, and viruses are used to create these with a variety of shapes and characteristics.[68] Although green nanoparticles have been shown to be environmentally beneficial and less hazardous, more stable, higher quality, and size shape homogeneity are still required.[69]

GREEN SYNTHESIZED NANOPARTICLES FROM PLANTS

Phytonic extracts are widely used to catalyse bottom-up mechanisms that result in the formation of nanoparticles from molecules and sub-nanosized particles. Recently, Silybummarianum has produced reducing agents for gold ion bio reduction.[70] Plant extract-based bio-reduction is faster than bacteria, fungi, or chemical techniques.[15] Phytonic extracts were used in the biosynthesis of metallic nanoparticles[71] to produce NPs of various shapes and sizes. Different plants and extracts can be used to create nanoparticles, and there is still much room for research in this area.[72]

The metal ions reduced and then nucleated is called as activation phase. Further, the small adjacent nanoparticles spontaneously coalesce into particles with increasing stability of nanoparticles is growth phase. Finally in the termination phase the final exact size of nanoparticles is estimated. Nanoparticles aggregates into nano prisms, nanotubes, nano hexahedrons, nanotubes, and cubical other irregularly shaped nanoparticles. Plant extract influences or controls the conformation and stability levels of nanoparticles during the termination phase.[73] Plant-mediated nanoparticle synthesis brings together nanotechnology and plants. This technology generates nanoparticles at room temperature, at a low cost, and in an environmentally friendly way. Biomolecules from plant extracts, as reducing or stabilising agents, promote rapid biogenic reduction of a metal ion under ambient conditions, as demonstrated in (Figure 5). Furthermore, research into nanoparticle interactions with biomolecules and microbes is advancing rapidly. Some of the metabolites from plants such as terpenoids, sugar, polyphenols, phenolic acid, alkaloids, and protein have important role in metal ion reduction into nanoparticles with stability. Nanoparticles have been successfully prepared from a variety of plant extracts and metal acids as well as salts, including gold, copper, silver, platinum, and irons.[74,75]

The nanoparticle is multifunctional and has applications in as the area of nutrition, medicine, and energy,[76] including therapy, diagnostics, surgical nanodevice creation, and commercial product manufacturing.[77] As reported in the studies the plant extracts can be used as a potential precursor to produce nanoparticles, despite the fact that they have been used for thousands of years with no adverse effects. Furthermore, due to their enormous variety and ease of availability, plant extracts, phytoconstituents have been extensively investigated for production of nanomaterials.[78]

A variety of secondary metabolites are present in plant extracts which acts as a reducing as well as stabilising agents in the formation of biofunctionalized metallic nanoparticles synthesis by bio reduction method. The available chemical and physical methods used in the synthesis of nanoparticles which is toxic to many organisms. Platinum, cobalt, silver, copper, gold, palladium, zinc, platinum, cadmium, magnetite, and nickel can be used in the synthesis of nanoparticles with isolated phytoconstituents from plants.

GREEN SYNTHESIZED NANOPARTICLES

Silver Nanoparticles

Silver nanoparticles (AgNPs) are antibacterial drugs and exhibit more wide action against all range of gram positive as well as gram negative bacteria including resistant. This wide range of action is due to the chemical stability, wound-healing capability, catalytic activity, high conductivity, and surface plasma resonance of AgNps.[79] Moreover, the use of plant extracts in the synthesis of silver nanoparticles is a single-step process for has initiated the considerable interest. Starch and chitosan are plant-derived polysaccharides that have recently been used to create silver nanoparticles. These stabilised nanoparticles also improve antimicrobial activity. Silver reduction is aided by amino acids, proteins, polysaccharides, secondary metabolites such as terpenoids, alkaloids, saponins, and other biomolecules.[80] Although AgNPs have many applications, their low stability precludes their use in some medical or sanitary settings. As a result, determining the material's shelf life under various storage conditions is critical. As investigated by Korshed *et al.* the antibacterial activities of laser-grown AgNPs against *E. coli* bacteria kept under cold, dark and daylight conditions exhibited the antibacterial activity lasted 266 to 405 days, more than that of chemically synthesised AgNPs.[81] Gauze impregnated with Ag-SiO_2 nanoparticles demonstrated greater antibacterial activity than the Ag-containing dressing available in the market for the infection control and treatment of superficial wounds against *E. coli* and *S. aureus*. Biopolymers, collagen and peptides are non-inflammatory and non-toxic in nature acts as a capping agent which reduces the toxicity of AgNPs whereas increases the efficacy as well as stability. Tanvir *et al.*[82] investigated the

antibacterial properties of AgNPs in a variety of morphologies, including spheres and prisms stabilised with PVP and coated with poly-L-arginine. Combining AgNPs with Grapheme Oxide (GO), another nanomaterial, results in improved antibacterial capabilities due to synergistic effects. GO has a layered two-dimensional structure.[1]

Zinc Nanoparticles

Green synthesis, which uses a biomimetic technique, allows for the large-scale synthesis of Zinc Oxide (ZnO) NPs without extra contaminants, and these NPs have higher catalytic activity while using less expensive and harmful ingredients.[83] The phytochemicals in the plant extract act as reducing, stabilising or capping agents. UV-Visible Spectrophotometric and FTIR studies confirmed the stability of ZnO NPs synthesised from flower extract of Trifolium pratense[84] and Rosa canina fruit extract. The extract acted as a reducing and stabilising agent, and the bio-capping was accomplished through the use of phenolic and carboxylic acid found in the fruit extract. Similarly, Aloe Vera leaf extract produced spherical ZnO NPs containing the plant's free carboxylic and amino groups.[85,86]

Copper Nanoparticles

K. Rayapa Reddy[87] described a green method for producing Copper Oxide (CuO) NPs that makes use of the asclepiadaceous plant *Calotropis procera*. Despite their short band distance, these nanoparticles are widely used in many applications, including catalysis and photocatalysis. Green synthesis of Copper NPs with the peel extract of *Punica granatum* where the peels were obtained, cleaned, powdered, and mixed with sterile water heated until the solution turned yellow reported by Alaa Y. Ghidan *et al.*[88]

Cerium Nanoparticles

The cerium NPs has been synthesized using *Gloriosa superba* leaves where 3.72 g of $CeCl_3$ added to the distilled and stirred at 80°C till 4 to 6 hr till the solution turned brown. Another study discovered that honey could be used to produce CeO_2 nanoparticles.[89,90]

Gold Nanoparticles

The Gold NPs (AuNPs) have applications in wide areas such as optical, biological, due to electronic and catalytic due to its uniform arrangements in terms of size and shape.[91] To date, a variety of methods for producing gold NPs have been developed, including electrochemical, physical, photochemical, and chemical reduction methods.[92] Around 10 gm of Fresh *Sphaeranthus indicus* leaves were placed in 100 mL of boiling double purified water and left for 10 min. For the Au NPs synthesis, 100 mL of 1mM $AuCl_4$ and 10 mL of *S. indicus* leaf extract, stirred for 30 min till light yellow-colored mixture turned wine red at pH 5.4.[93,94]

METALLIC NANOPARTICLES CHARACTERIZATION TECHNIQUES

Metallic nanoparticles synthesized in various shapes and sizes and having its separate UV-VIS absorption peak. Metals with high absorption peaks, such as copper, silver, and gold, are employed. Structural studies including size, shape and size distribution has been determined by using scanning electron microscopy and transmission electron microscopy. X-ray diffraction was used to investigate the crystal structure and Energy dispersive X-ray spectroscopy is used to determine the identity, purity, and elemental composition of manufactured nanoparticles. Dynamic light scattering was used to examine particle size distribution and zeta potential, and zeta potential was determined using Malvern zeta sizer nano range equipment. More stable nanoparticles have zeta particle values greater than or equal to +25mV or -25mV. Chemical structure and functional groups have been studied by Fourier transform infrared spectroscopy.[95]

Applications of NPs

AgNPs are highly disrupting cell membrane polymer subunits; there is a disturbance in protein synthesis mechanism and break cell wall membrane due to repellent action of NPs. Green synthesised metallic nanoparticles have more potential than amphotericin and fluconazole. There is a decrease in the effectiveness of antifungal agents, as well as some side effects such as nausea, liver damage, increased body temperature, renal failure, and so on. AgNPs are active in destroying fungal growth. Enzymes and non-enzymatic molecules both regulate the production of free radicals. Cancer, atherosclerosis, and brain damage are all examples of cellular damage caused by free radicals. Enzymatic and non-enzymatic antioxidants can aid in the diagnosis of a wide range of chronic illnesses, including neurodegeneration, diabetes, cancer, AIDS, metabolic disorders, and nephritis. In general, nanoparticles, particularly tea extracts containing flavonoids and phenolic groups, have excellent antioxidant properties. The NPs are used to inhibit cell growth and regulate the process of the cell system. NPs regulate cancer cells such as the Hela cell line, HCT116, and Hep 2. Free radicals stimulated normal cell function and proliferation. Green synthesis nanoparticles regulate free radical generation in cells. Silver nanoparticles produced by plants have an impact on enzymes and the cell cycle in the circulation. Interestingly, in the medical field, metallic nanoparticles cure many retroviral illnesses and cancers without interfering with normal cells, whereas bio-based nanoparticles remove the malignant deposit. Diabetes mellitus is defined as an increase or decrease in blood sugar levels. Sugar levels in the blood can be controlled using insulin, food, and diet. Diabetic patients benefit from gold NPs. The use of AuNPs in diabetic mice reduces the elevated levels of enzymes present in the liver such as uric acid, transaminase, serum creatinine, and alkaline phosphatase. NPs have a good pharmacological action

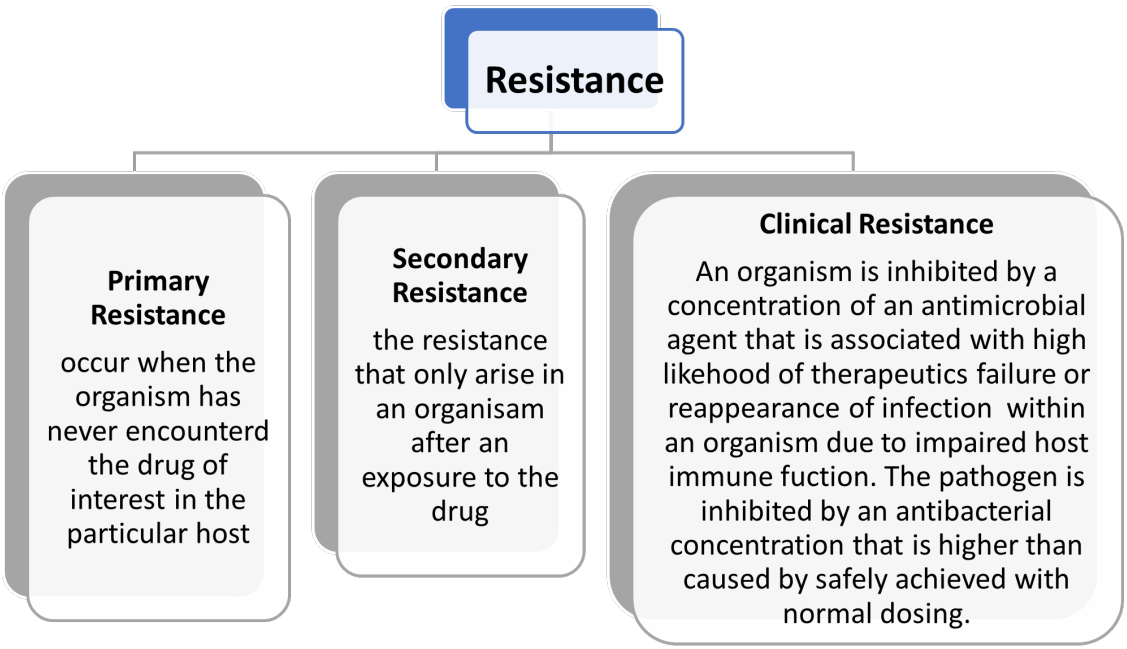

Figure 1: Types of Microbial Resistance.

in controlling diabetic Mellitus, with only minor side effects. Plant-mediated NPs are used to control viral pathogen growth in the body. AgNPs are used to control viral infections. Because of its multiple binding sites, to control the virus the MNPs bind with gp120 of the viral membrane. MNPs are effective against both cell-associated and cell-free viruses.[43]

COMBINATIONAL ANTIMICROBIAL CHEMOTHERAPIES

The prevention of antibiotic resistance is possible and more effective with a combination approach of plant extract with antibiotic that give synergistic interaction.[96] Plant-derived chemicals have been shown to improve the antibacterial potency of conventional antibiotics in the literature. When ß-lactams were combined with mangosteen from mangosteen fruit,[97,98] quercetin, or kaempferol, antibiotic efficiency was increased in ß-lactam resistant bacterial strains.[99] As a result, plant chemicals' ability to repurpose conventional medicines for microbial diseases may have a significant impact on global health in terms of combating antibiotic-resistant pathogenic bacteria.[99] Aqueous extracts of *Eichhornia crassipes* used to synthesize the silver nanoparticles and its combination with antibiotics such as penicillin, VAM, streptomycin and tetracycline demonstrated synergistic activity. Moreover, silver nanoparticles reinforced the antibacterial effects of antibiotics against susceptible as well as resistant bacteria. Several studies demonstrated the synergistic effect of conventional antibiotics with crude plant extracts. Ahmad *et al.*[100] reported that medicinal plants extracts were synergistic with ciprofloxacin and tetracycline against extended-spectrum -lactamases producing MDR-enteric bacteria. Methanolic extracts of *Brassica oleacera*,

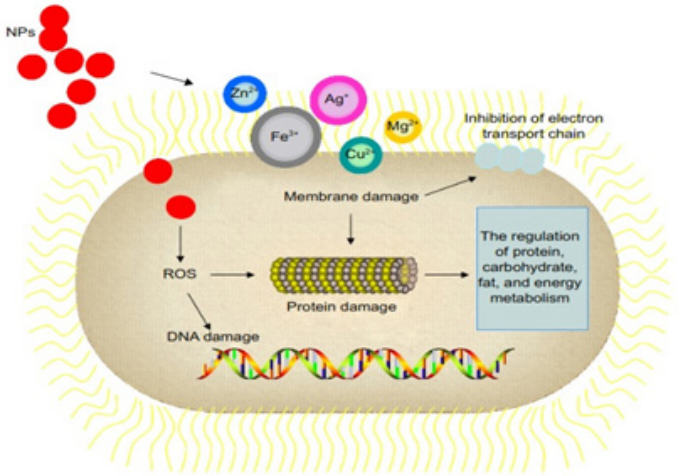

Figure 2: Mechanisms of Action for Metallic Nanoparticles (NPs) in Bacteria.[47]

Capsicum frutescens, and *Basilicum polystachyon* exhibited synergistic effects with tetracycline, cefepime, streptomycin, ciprofloxacin, norfloxacin, chloramphenicol, ampicillin, erythromycin, and kanamycin against MDR Gram-negative bacteria.[101]

Phytochemicals are multi-targeted due to their structural variety, which separates them from the features of traditional antibiotics. Despite the fact that people have been utilising plant products for millennia, there is no indication of bacterial resistance to these phytochemicals.[6] Efflux pump inhibitors may have a bigger impact since they can repurpose a larger range of medicines because efflux pumps frequently expel several drugs from the cell. The use of extracts produced from commonly used plants as antimicrobial potentiators in the treatment of

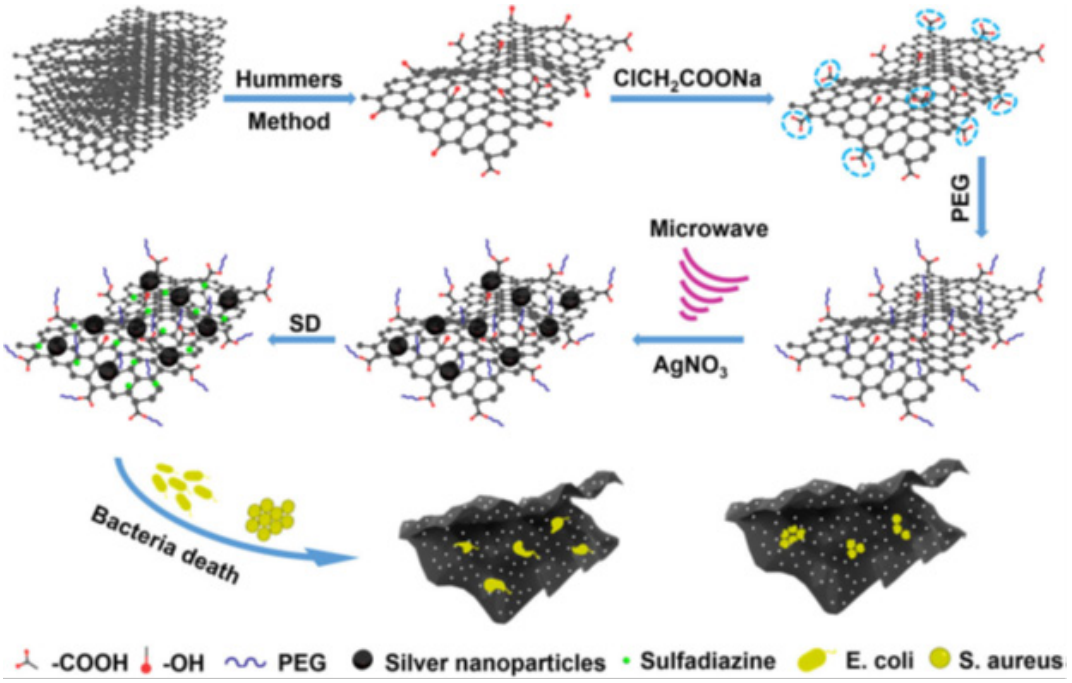

Figure 3: Preparation of antibacterial material.[76]

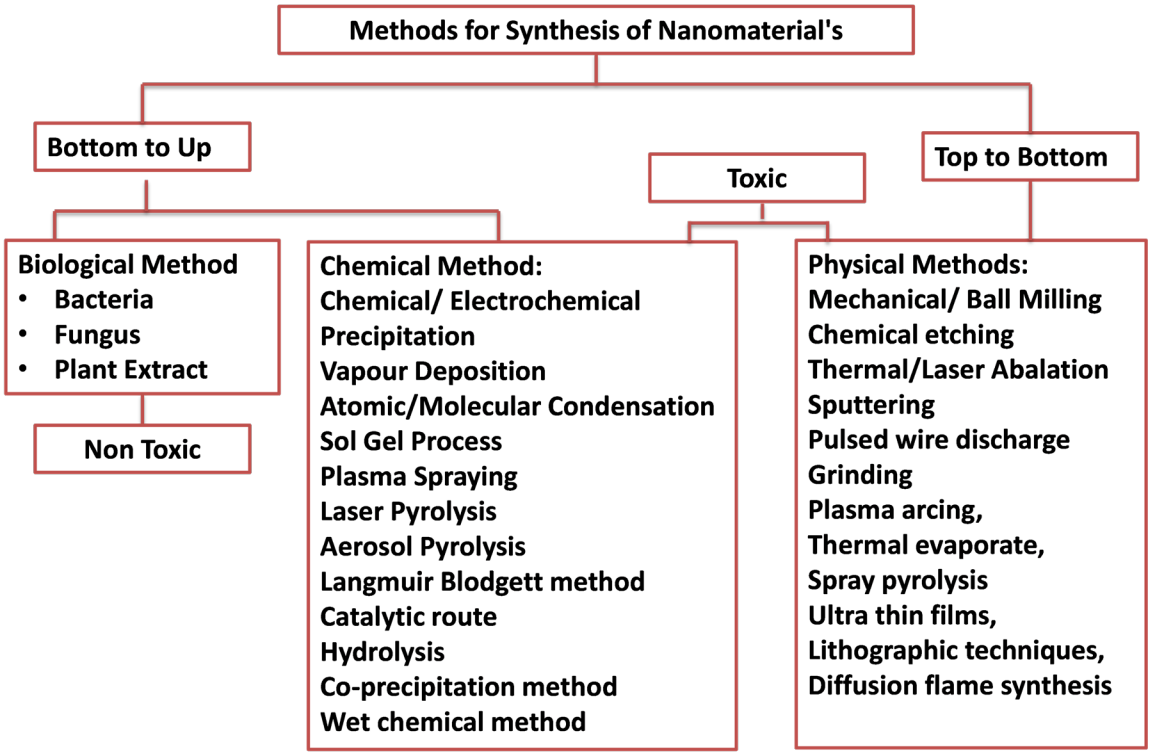

Figure 4: Methods for Synthesis of Nanomaterial.

extremely resistant infectious illnesses. Silver nanoparticles exhibits better antimicrobial efficacy against MDR bacteria, viruses, and microorganisms therefore it has been considered for extensive research.[102] *Curcuma longa* extract used to synthesize palladium particles which are nano-crystalline in nature with 10–15 nm size as a biomaterial. Stable Cu nanoparticles (40–100 nm) biosynthesized using *Magnolia* leaf extract showed higher antibacterial activity against *Escherichia coli*.[15] Similarly, zinc inhibits bacterial enzymes like dehydrogenase, thiol peroxidase, and glutathione reductase.[32]

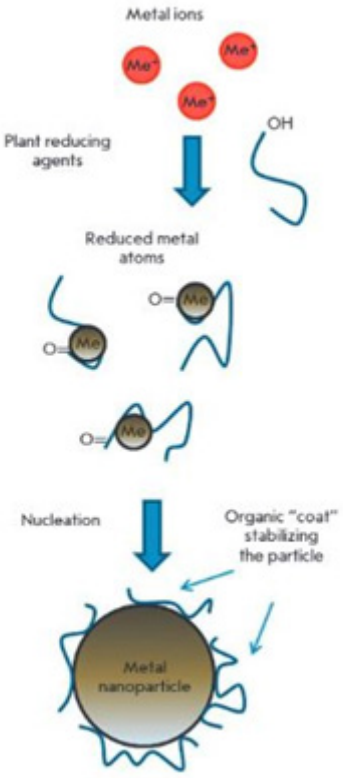

Figure 5: Process of Metal Nanoparticles Synthesis in a Plant Extract.[88]

Antimicrobial Peptides (AMPs) are functional building blocks that are found in the innate immune system and have a role in protecting the host from invading pathogenic microorganisms. They are classified as -helical, -sheet, or extended forms. The sequences, secondary structures, charged density, hydrophobic residues, antibacterial mechanisms, and reported drug resistance in natural and artificially screened AMPs have been studied. Furthermore, because of their improved presentation in drug-resistant patients, AMPs are currently being considered as prospective antibiotic substitutessss.[50] Plants have been effectively exploited in the production of different green synthesized nanoparticles such as cobalt, nickel, copper, cadmium, silver, palladium, gold, platinum, zinc and magnetite, according to Kuppusamy *et al.*,[60] and these plant-mediated nanoparticles are possible cures for illnesses such as malaria.

Vahdati and Tohidi[103] used a nanohybrid system to study the antibacterial activity of selenium nanoparticles.[104,105] The compounds from transition metals such as silver and silver salts, are among the most researched options for combating sensitive as well as resistant bacteria.[106,107] Metal nanoparticles, particularly silver nanoparticles, have been employed for antibacterial, antibiofilm, larvicidal and insecticidal effects, and anticancer activities in a number of medicinal applications.[108] Combinatorial formulations of transition metals, such as the use of biopolymers as capping agents of metallic nanoparticles to generate bio composites, have been proposed to overcome metals' harmful nature.[109] The intrinsic hydroxyl functionality of cellulose is considered in the creation of a new silver NPs bio composite in this study.[110]

The majority of contemporary metal NP production methods rely on the reduction of cations, which results in nanostructures that can be tuned in size and form. Specifically, gold ions in salt are reduced to generate AuNPs via chemical techniques. Reducing chemicals such as citrate, ascorbate, borohydride, or amines are used to reduce gold salts. Additionally, stabilisers are required to avoid AuNP aggregation. Citrate and alkanethiols are all-purpose stabilising agents among the numerous stabilising agents. Because various sizes and shapes of AuNPs have varying optical and electrical properties, size control is essential for obtaining homogenous particles. Changing the pH and chemical reagent ratios, as well as employing physical factors, can help achieve this.[110]

The surface chemistry of NPs has a big impact on how they interact. As a result, metal NP surfaces are frequently changed and functionalized to suit their intended use. Improvement of *in vivo* stability, prevention of aggregation, and avoidance of absorption by the reticuloendothelial system, toxicity control, and optimization for clinical diagnostic and targeted applications are all aims of functionalization. Chemical or biological substances can bind to AuNPs via electrostatic adsorption or chemical reactions. Because AuNPs have a negatively charged surface, they will adsorb positively charged substances such as cysteine and -amyloid peptides in acidic pH. Because thiol groups are known to make chemical interactions with gold atoms, AuNPs are often connected to other chemical and biological compounds. Another benefit of nanoparticles is their effectiveness in detecting harmful bacteria and biomarkers of malignant tissues *in vivo* and *in vitro*.[111] In another study, liposomes were employed to increase the stability of encapsulated nisin against pH and temperature extremes, allowing it to be used in food preparation. Phyto glycogen NPs, chitosan, pectin, and alginate are all popular peptide NPs carrier materials. NPs have a wide range of uses, having been used successfully in bio detection systems as sensors and diagnostic platforms with higher sensitivity and selectivity. Because the transduction mechanisms offered by NPs have shrunk in size, most of these platforms have found use at the point of need and/or point of care.[111]

CONCLUSION

Repetitive use of antibiotics makes the microorganisms resistant to the treatment which leads to an increase in the dose of an antibiotics for further treatment. The increased dose of antibiotics may lead to toxicity. Although the continuous use of traditional medicines such as curcumin, fenugreek, neem, and different phytochemicals has not developed any resistance and has not shown any toxicity. Moreover, the metals also exhibited

antimicrobial activity in nano size. Therefore, the plant extract synthesized metallic nanoparticles as a biofunctionalized NPs has been established as a promising tool for decades to address the issue of rapidly increasing the incidence of MDR. Combinatorial approach of green synthesized nanoparticles with antibiotics may prevent microbial drug resistant and improve the efficacy of antibiotics in resistant microbes. Metallic nanoparticles derived from plant extracts could act as a synergist and may provide an alternative to address the issue of microbial drug resistant. The future of this green synthesized nanoparticles outlined as a shifting of lab scale work to industrial scale, more involvement of bioinformatics for elucidation of phytochemicals in the NPs, identifying the toxicity profile and the most importantly evaluation of exact mechanism of action against resistant microorganism as these NPs have major applications in the field of medicine, cosmetics and food industries.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MDR: Multidrug Resistance; **WHO:** World Health Organization; **AMR:** Antimicrobial resistance; **VAM:** Vancomycin; **MNPs:** Metallic Nanoparticles; **AgNPs:** Silver Nanoparticles; **GO:** Graphene oxide; **ZnO:** Zinc oxide; **CuO:** Copper oxide; **AuNPs:** Gold NPs; **AMPs**: Antimicrobial peptides, **TMNPs:** Theranostic Metallic Nanoparticles.

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