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Review article

A review on green synthesis of silver nanoparticle and zinc oxide nanoparticle from different plants extract and their antibacterial activity against multi-drug resistant bacteria

Sumon Das, Tamalika Chakraborty*

Department of Life Science, Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata-700114, West Bengal.

Key words: Green synthesis, Plant extract, Silver nanoparticle, Zinc Oxide nanoparticle, Multi-Drug Resistant Organism.

***Corresponding Author: Tamalika Chakraborty,** Assistant Professor, Department of Life Science, Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Road, Panihati, Kolkata-700114, West Bengal.

Mobile: 9674932502

Email id: tamalika.chakraborty@gnipst.ac.in

Abstract

The green synthesis of the nanoparticle is a fascinating field of modern science. Biosynthesized nanoparticles are much stable and varied in size, shape, and now they are applied in the various field along with the therapeutic application. Different types of metallic nanoparticles are synthesized by Green Technology, but among them, Silver (Ag) and Zinc Oxide (ZnO) nanoparticle have unique properties like Ag np has high conductivity, localized surface plasma resonance, chemical stability and catalytic activity; besides, Ag np has demonstrated tremendous broad-spectrum activity against Multi-Drug Resistant (MDR) bacteria. Additionally, ZnO np showed charismatic antibacterial properties because of its surface reactivity, and it resulted when the particle size was reduced. Reduction of the particle size increased its specific surface area making it a proper antibacterial agent. ZnO np is a non-bio toxic material with photocatalysis and photo-oxidising properties on biological species. ZnO np produce ROS which interacts with the cell membrane of bacterial species, which leads to the inactivation of genetic materials. These properties of Ag and ZnO np makes them a suitable option to the scientists for developing medicines to prevent Multi-Drug Resistant (MDR) microorganisms. Metallic nanoparticles like Silver (Ag) and Zinc Oxide (ZnO) can be produced by the green synthesis method (using plant parts) and synthesized Nano-particles are applied to prevent MDR organisms. This paper highlights on the synthesis of Silver (Ag) nanoparticle and Zinc Oxide (ZnO) nanoparticle from the different plant source and their use in biomedical science and others fields.

Introduction

In current days microbial infection became a Global concern and significant cause of morbidity and mortality because of the development of resistant strains of a virus, bacteria, pathogenic fungi, protozoa and they can survive the clinical treatment with the antibiotic, antifungal, antiviral, antiprotozoal drugs [1]. Highly potent antibiotics like fluoroquinolones and aminoglycosides can generate various effects, and they are retained only for critical infectious diseases. In present days, the growth of antibacterial resistant organisms results in the creation of newly developed methods for combating antibacterial drug resistance [2].
Nanotechnology is a conception of handling and the usage of resources having a size range of 1-100 nm, and they are known as Nanoparticle. In recent years, scientists concentrated their focus on nanoparticles due to their different magnetic, optoelectronic and physicochemical properties that are regulated by their size and shape distribution [3].
In present days as an antibacterial agent Nanoparticles are used, and they are highly effective and acquire huge attention as they satisfy the requirements where antibiotics fail to prevent the development of Multi-Drug Resistant (MDR) mutants [4-5]. Nanoparticles are used in different applications like catalysts, chemical sensors, electronic components, imaging for medical diagnostic and medical diagnostic protocols, pharmaceutical products, drug delivery (various nanoparticle platforms especially liposomes, polymeric nanoparticles, inorganic nanoparticles and dendrimers have acquired significant attention) because of their novel properties like physical, chemical and optoelectronic properties [6].
Antibacterial nanoparticles, i.e. metal and its oxide, and organic nanoparticles have several modes of action. In general, nanoparticles act in four lethal pathways, and these pathways are linked to each other, and in many situations, they coincide.

I. Disrupt the integrity and membrane potential.
II. Formation of reactive O_2 species and induction of Nitrogen reactive species.
III. Inhibition of several specific enzymes.
IV. Results in the programmed cell death.

In this paper, the green synthesis of Ag and ZnO nanoparticle from a different plant extract and their antibacterial properties against the Multi-Drug Resistant bacteria are reviewed.

Nanotechnology is a branch of technology that deals with tremendously fine particles and having a length between 1-100 nm (sometimes higher than 100 nm) and having a three-dimensional structure. Nanotechnology, a different area of study field with a vast scale of application in cancer therapy, targeted drug delivery, electronics, cosmetic industry and biosensors [7]. At the end of 1970s Silver nanoparticles were used to treat the infectious diseases caused by pathogenic microorganisms during the diagnosis of orthopaedic disorders, resulting in quicker bone recovery. Several noble metallic nanoparticles are available for their exclusive properties like favourable chemical stability, catalytic activity, electrical conductivity, and antimicrobial activity such as antibacterial, antiviral, antifungal [8].

Furthermore, anti-inflammatory activities are combined into composite cryogenic superconducting materials, cosmetic product, food industry, electronic components have attracted distinct attention [9]. Due to antibacterial properties, the pernicious nature of Ag-np against several microorganisms (pathogenic bacteria) has been well known. Ag nanoparticle used in dental resin composites, coating for medical equipment and ion exchange [10-11]. Ag nanoparticle also applied in biomedical applications like wound dressing, topical medicines, antiseptic sprays, and fabrics. As antiseptic, silver nanoparticles disrupt the unicellular membrane of the microorganism and deactivate their cellular enzyme. Green synthesis of Ag nanoparticles was established by using plants, microbes and other biopolymers [9]. ZnO nanoparticles belong to the commercially applied inorganic materials because of their unique properties like electronic, structural, thermal, semiconducting, optical, piezoelectric properties. In case of stability, organic reagents are more unstable than ZnO nanoparticles. ZnO based nanomaterials have been studied for a vast diversity of applications such as catalysts, sensors, opto-electron, highly functional and effective photoelectron devices. ZnO nanoparticle has the vast surface area with an excessive catalytic activity which is a considerable advantage to use it in medical and pharmaceutical applications [12].

Antibacterial agents like antiseptics, antidandruff shampoos, baby powder, calamine powder contain ZnO nanoparticle. Few mechanisms of ZnO nanoparticle were identified:

I. ZnO nanoparticle generates hydrogen peroxide, this can penetrate through the cell membrane, and it injured the cell and prevented the development of the cells [13].

II. The antibacterial property of the ZnO nanoparticles based on the affinity between the ZnO and bacterial cells [14].

Bacterial enzymes like dehydrogenase and specific protective enzymes like glutathione reductase and thiol peroxidase are inhibited by the ZnO nanoparticles [15]. ZnO nanoparticles interact with the membranes of microorganisms (bacteria) and act as a potential antibacterial agent because of their excellent reactivity. Antibacterial property of the ZnO nanoparticles based on the concentration, size and healing temperature. ZnO nanoparticles is an ideal potential antibacterial reagent to replace some antibiotic due to selective toxicity and are generally considered as a safe reagent to human and animals [16, 17].

Green synthesis of the Ag nanoparticle using plant extract

Usage of the plant for the nanoparticle synthesis does not require the maintenance of cell culture, and it supports the large-scale production of nanoparticle which is a valuable benefit in this field. Production of extracellular nanoparticle depends on the usage of plant leaf rather than the entire plant [18]. Plant extract holds various active biomolecules like alkaloids, phenolic acids, sugars, proteins, polyphenol and terpenoids. These active biomolecules have a crucial part in this biological reduction; first, it reduces and stabilizes the metallic ions [19-20]. Size and morphology of the produced nanoparticles based on several factors like the plant extract concentration, metal salt concentration, reaction time, temperature and pH of the reaction mixture [21-22]. Synthesis of the Ag nanoparticle by the usage of plant extract has several benefits due to its eco-friendly, rapid, economical, non-pathogenic protocol. A huge number of plants are used to synthesize the Ag nanoparticles and are stated in table 1 [23-24]. Plants parts should be taken, like the leaf of the plant, and then washed thoroughly by normal water followed by distilled water to eliminate the debris. Then these fresh leaves must be placed in the shaded region for 10-15 days for drying and then it should be powdered with the help of a domestic blender. Plant extract should be organized by adding around 10 gm of dried powder into 100ml of deionized distilled water. The synthesized infusion placed for the filtration carefully until no insoluble substance appeared in the broth. Then standard $AgNO_3$ solution must be prepared followed by adding the few ml of desired plant extract, and it will be converted to desired Ag nanoparticle, and the reaction mixture was subjected to UV-visible spectra at a regular interval to check the production of Ag nanoparticle [24].

Table 1. Green synthesis of silver nanoparticles using different plant extracts [9-11, 23-24, 27-30].

Plants	Plant parts	Size	Shape
Averrhoa carambola	Leaf	14	Spherical
Acorus calamus	Rhizome	19	Spherical
Aristolochia indica	Leaf	30-55	Spherical Or Cubical
Aloe vera	Leaf gel	5-50	Octahedron
Annona muricata	Leaf	22-53	Spherical
Abutilon indicum	Leaf	106	Crystalline
Aerva lanata	Leaf	18.62	Spherical
Alstonia scholaris	Bark	50	Spherical
Azadirachta indica	leaf	20	Triangular
Artocarpus heterophyllus	Seed	10.78	Spherical And Irregular
Alternanthera dentate	Leaves	50-100	Spherical
Argyreia nervosa	Seeds	20-50	Spherical
Acalypha indica	Leaf	20-30	Spherical
Allium sativum	Leaf	4-22	Spherical
Aloe vera	Leaf	50-80	Spherical And Triangular
Boerhaavia diffusa	Whole plant	25	Spherical
Brassica rapa	Leaf	16.4	Spherical
Clerodendrum serratum	leaf	5-30	Spherical
Carica papaya	Leaf	25-50	Spherical
Cucurbita maxima	Petals	19	Crystalline
Calotropis gigantea	Latex	5-30	Spherical
Crataegus douglasii	Fruit	29.28	Spherical
Cocos nucifera	Coir	22	Spherical
Cymbopogan citratus	Leaf	32	Spherical
Calastropis procera	Plant	19-45	Spherical
Centella asiatica	Leaf	30-50	Spherical
Coccinia indica	Leaf	10-20	Spherical
Citrus sinensis	Peel	10-35	Spherical
Datura metel	Leaf	40-60	Spherical
Euphorbia helioscopia	Leaf	2-14	Spherical
Enteromorpha flexuosa	Seaweed	2-32	Circular
Eucalyptus chapmaniana	Leaf	60	Spherical
Eclipta prostrate	Leaf	35-60	Triangles, Pentagons, Hexagons
Eucalyptus hybrid	Peel	50-90	Pherical
Ficus carica	Leaf	21	Crystalline
Grewia flaviscences	Leaf	50-70	Spherical
Garcinia mangostana	Leaf	35	Spherical
Hypnea musciformis	Leaf	40-65	Spherical
Hemidesmus indicus	Leaf	25.24	Spherical
Helicteres isora	Root	30-40	Crystalline
Hydrastis canadensis	Whole plant	111	Spherical
Justicia adhatoda	Leaf	5-50	Spherical
Lansium domesticum	Fruit	10-30	Spherical
Lycopersicon esculentum	Fruit	10-40	Spherical
Moringa oleifera	Leaf	11	Rectangle
Momordica cymbalaria	Fruit	15.5	Spherical
Mukia maderaspatana	Leaf	13-34	Spherical
Myrmecodia pendan	Whole plant	10-20	Spherical
Musa balbisiana	Leaf	50	Spherical
Morinda citrifolia	Root	30-55	Spherical
Melia dubia	Leaf	35	Spherical
Musa paradisiacal	Peel	20	Spherical
Memecylon edule	Leaf	20-50	Triangular, Circular, Hexagonal
Nelumbo nucifera	Root	16.7	Spherical, Triangular
Onosma dichroantha	Root	5-65	Spherical
Ocimum tenuiflorum	Leaf	50	Cuboidal
Prunus yedoensis	Leaf	20-70	Circular, Smooth Edges

Plukenetia volubilis	Leaf	4-25	Optical
Prosopis farcta	Leaf	10.8	Spherical
Piper longum	Fruit	46	Spherical
Potentilla fulgens	Root	10-15	Spherical
Phytolacca decandra	Whole plant	90.87	Spherical
Pistacia atlantica	Seeds	10-50	Spherical
Premna herbacea	Leaf	10-30	Spherical
Psoralea corylifolia	Seeds	100-110	Spherical
Portulaca oleracea	Leaf	60	Spherical
Pogostemon benghalensis	Leaf	80	Spherical
Quercus brantii	Leaf	6	Spherical
Rosmarinus officinalis	Leaf	10-33	Spherical
Skimmia laureola	Leaf	46	Hexagonal
Saraca indica	Leaf	23	Spherical
Sinapis arvensis	Seed	14	Spherical
Swietenia mahogani	Leaf	50	Spherical
Tephrosia tinctoria	Stem	73	Spherical
Tribulus terrestris	Fruit	16-28	Spherical
Thevetia peruviana	Latex	10-30	Spherical
Trachyspermum ammi	Seeds	87, 99.8	Spherical
Vitex negundo	Leaf	20	Cubic
Vitis vinifera	Fruit	30-40	Spherical
Ziziphus jujuba	Leaf	20-30	Crystalline
Ziziphora tenuior	Leaf	8-40	Spherical

Green synthesis of Ag nanoparticles along with the factors affecting the synthesis

Effects of pH
Synthesis of the Ag nanoparticle depends on the pH of the reaction medium, which plays a crucial role during synthesis [25]. Synthesis of the Ag nanoparticle occurs promptly between the basic to neutral pH range. Development of the Ag nanoparticles is delayed by acidic conditions or an acidic pH, and it is enhanced by the basic pH or in basic condition. Lower pH or the acidic pH results in larger nanoparticle whereas small shaped spherical nanoparticle formed in the basic pH [26]. For example, *Cinnamon zeylanicum* bark extract was used to synthesize the Ag nanoparticles, a higher concentration of the bark extract with pH 5 and above, forms the higher amount of spherically shaped nanoparticle and having a size range of 8-20 nm [27].

Effects of reactant concentration
During synthesis, the biomolecule concentration of the plant extract regulates the shape or structure of the nanoparticles. For example: Octahedron shaped Ag nanoparticle was formed from the leaf extract of *Aloe vera*, whereas hexagonal and spherical shaped Ag nanoparticle was formed from the seed extract of *Mangifera indica*, here the leaf gel extract of *Aloe vera* contains flavanones terpenoids, and Gallo tannins, tannins and phenolic compounds, are present in the seed extract of *Mangifera indica* [28].

Reaction time and temperature
A recent study discovered that the temperature and reaction time influence the size and shape of the nanoparticle. For example, a mixture of leaf extract of *Azardirachta indica* and $Ag(NO)_3$ when combined, it forms larger nanoparticle with increasing reaction time. The time of the reaction was set between 30 min and 4hr to develop a variation in the size of the practice in between 10 to 35 nm [29]. Ag nanoparticle synthesized from the *Citrus sinensis* peel extract having an average size of approximately 35 nm, at the reaction temperature of 25°c and the size of the particle decreased to 10 nm when the reaction temperature increased to 60°c [30].

Antibacterial activity of silver nanoparticle
Today, Antibiotic-Resistant microbes are the growing global threat, certain MDR pathogens like gram-positive and gram-negative bacteria (table 2) are responsible for some infections which increase the death rate and treatment cost in undeveloped countries and today biomedical science need more advancement for the education and the creation of unique antibacterial agents which are more potent to encounter the MDR strains [26]. Metallic nanoparticles are governed to inhibit the development of the growth of the Multi-Drug Resistant organism because they can prevent their growth. Properties like physical, chemical, thermal, electrical and optical are the main factors in their selection. Certain gram-positive and gram-negative bacteria which belong to the MDR pathogen groups are responsible for certain infections which increase the death rate and treatment cost in undeveloped countries [31-32].

Table 2. Multi-Drug Resistant microbes [31, 32].

Bacterial strains	Resistant to
GRAM-POSITIVE	
Bacillus subtilis	Chloramphenicol Erythromycin Lincomycin Penicillin Streptomycin Tetracycline
Corynebacterium diphtheriae	β-lactam antibiotics Chloramphenicol Tetracycline Trimethoprim Sulfamethoxazole
Enterococcus faecium	Vancomycin Gentomicin
Listeria monocytogenes	Erythromycin Gentomicin Kanamycin Rifampin Streptomycin Sulfamethoxazole Tetracycline
Staphylococcus aureus	Methicillin Vancomycin
Streptococcus pneumonia	Penicillin Erythromycin
Streptococcus pyogenes	Erythromycin macrolides
GRAM-NEGATIVE	
Acinetobacter baumanii	Carbapenems Imipenem
Escherichia coli	Ampicillin Cephalosporins Chloramphenicol Fluoroquinolones Nalidixic acid Rifampin Sulfamethoxazole Streptomycin Tetracycline
Klebsiella pneumonia	Carbapenems Imipenem
Pseudomonas aeruginosa	β-lactams Chloramphenicol Fluoroquinolones Macrolides Novobiocin Sulfonamides Tetracycline Trimethoprim
Shigella flexneri	Ciprofloxacin Nalidixic acid
Vibrio cholera	Fluoroquinolones Tetracycline

In the entire world, the Ag nanoparticle has been applied popularly for various purposes. The antibacterial effectiveness of Ag nanoparticles is strongly determined by their shape, size, concentration and colloidal state. It was established by the scientist that the reduction of the size of Ag np increased the stability and biocompatibility of Ag np. Antibacterial effectiveness of Ag nanoparticles is strongly determined by their shape, size, concentration and colloidal state [33]. As a well-recognized antibacterial agent, silver is used against several types of microorganisms like bacteria, fungi, and viruses. Ag has been defined as a healing agent for several diseases in Ayurveda [34]. Commonly Ag is applied in their nitrate form as an active antibacterial agent, but when the Ag nanoparticle is applied as an antibacterial agent, it is more effective than Silver Nitrate because Silver nanoparticle has more surface area than Silver Nitrate (table 3) [35]. Silver nanoparticles are coupled with four distinct antibacterial actions [36]:

I. Attachment of the Ag nanoparticles on the surface of cell wall and membrane.
II. An incursion of the Ag nanoparticles within the cell results in the destruction of the structures within the cell-like mitochondria, vacuoles, ribosomes, and biomolecules like lipids, protein, and DNA.
III. Ag nanoparticles yield the reactive oxygen species (ROS) and free radicals which stimulate the oxidative stress and cellular toxicity.
IV. Regulate the signal transduction pathway.

Table 3. Antibacterial activity of Ag nanoparticle [36-44].

Bacterial strains	Ag NP size(nm)	Mode of action
GRAM-POSITIVE		
Bacillus subtilis	5	Cell membrane damage: outflow of the reducing sugars
	10	Degeneration of chromosomal DNA; increasing level of Reactive Oxygen Species
Clostridium diphtheria	28.42	Rupture of cell wall;Structural loss of proteins
Listeria monocytogenes	-	Penetration the bacterial cell
	23±2	Functional deactivation of the electron transport chain; increasing level of Reactive Oxygen Species at the cell membrane
Staphylococcus aureus	-	Adhesion to cell wall; separation of cell membrane from the cell wall; condensation of DNA; replication inhibition; proteins inactivation
	5	
		Damage of the Cell membrane; outflow of reducing sugars
	25	
		Interact with the cell membrane and S- and P-containing compounds; blockage of respiration
GRAM-NEGATIVE		
Escherichia coli	5±2	Interact with cell membrane and S- and P-containing molecules attach to cell wall;
	-	
		separation of cell membrane from the cell wall; condensation of DNA; replication Inhibition; proteins inactivation
	10	
		Interact with S- and P-containing molecules
	5	
		damage of the cell membrane; outflow of the reducing sugars
	1-10	
		Interact with the cell membrane results increasing permeability; inappropriate transport activity; outflow of
	25	cellular elements
	16	Interact with S- and P-containing molecules
	-	Interact with the cell membrane; interact with S- and P-containing molecules
	9.3	Disruption of ribosomes; inhibition of translation; preventing the ATP formation by inactivating the functional enzyme
		Interaction with the cell membrane
Klebsiella pneumonia	<50	Interaction with DNA; preventing the of cell division
Pseudomonas aeruginosa	5±2	Interaction with the cell membrane and the S- and P-containing molecules
	10	
		Penetrating the cell
	28	
		Reduction of quorum sensing property of the bacteria
Salmonella typii	5±2	Interact with the cell membrane and the S- and P-containing molecules
	2-23	
		lysis of the cell wall
Vibrio cholera	5±2	Interact with the cell membrane and the S- and P-containing molecules
	90-100	
		Retardation of the metabolic pathways

Microorganisms, when treated with Ag nanoparticles, results in binding of nanoparticles on the cell wall which leads to morphological changes like shrinkage of the cytoplasm and membrane separation which directs the busting of the cell wall [37]. The integrity of the lipid bilayer and the cell membrane permeability are destroyed by the Ag nanoparticles when it reacts with the sulfur-containing enzymes which present within the cell wall and this interaction completely change the cell wall morphology [38]. Also, composition and width of the microbial cell wall also regulate the antibacterial property of Ag nanoparticles. The gram-positive bacterial cell wall is much thicker than the gram-negative bacterial cell wall, and the amount of peptidoglycan present in the gram-positive bacterial cell wall is much higher than the gram-negative bacteria. Positively charged Ag nanoparticles when applied to the gram-positive bacteria, it deposited on their cell wall due to the presence of high negative charges [31].

Furthermore, Ag nanoparticles are more lethal against the gram-negative bacterial species due to the presence of a thinner cell wall and the presence of a small amount of peptidoglycan. Therefore, they are used for better antibacterial treatment against the gram-negative bacteria. In addition, the cell membrane of gram-negative bacteria contains lipopolysaccharide layer, which contributes the negative changes on the cell membrane, and this LPS molecules boost the binding of the Ag nanoparticles and make bacteria more sensitive against Ag nanoparticle-mediated antibacterial treatment (table 3). For example, *S. aureus* a gram-positive bacterium which is less prone to the Ag nanoparticle than *E. coli*, which is a gram-negative bacterium [32, 23].

Ag nanoparticle destructs the intracellular structures and biomolecules in various ways. Firstly, suppression of translation is done by Ag nanoparticles by the denaturing the translational machinery ribosome. Secondly, Ag^+ denature the protein molecules by deactivating their functional groups. Furthermore, Ag nanoparticles and Ag^+ also disrupt the disulphide bonds on the active site of an enzyme, which results in the cell death. Ionized form of the Ag nanoparticle also has the capability of forming a complex with nucleosides of nucleic acid rather than developing a complex with phosphate groups of the nucleic acid (table 4). Ag^+ ions also act as an intercalating agent and denature the DNA molecule, which results in the cell death [39-41].

Ag nanoparticle act as an antibacterial, antifungal and antiviral agent, because it can produce the reactive oxygen species (ROS) like Hydrogen peroxide (H_2O_2), Superoxide anion (O_2^-), Hydroxyl radical (OH•), Hypochlorous acid (HOCl) and Singlet oxygen (O_2) and generation of these radicals within the cell by Ag nanoparticle results in the cell death [42-43]. Phosphorylation of several proteins or enzyme molecules in a bacterium is an important process; this process is inhibited by Ag nanoparticles by dephosphorylating the protein or enzyme molecules which results in the cell death [44].

Table 4. MIC of Silver nanoparticle against pathogenic bacteria [40].

Nanoparticle	Size (nm)	Organism tested	MIC	Proposed mechanism
Silver	21	*E. coli* *Vibrio cholerae* *Salmonella typhi* *P. aeruginosa*	All reduced 100% at 75µg/ml	Disruption of the cell membrane, Ag+ ions affect the DNA replication
Silver	50	*E. coli*	Reduced 99% with 0.1 µg/ml added to the agar surface	Disruption of the cell membrane, Ag+ ions affect the DNA replication
Silver	12	*E. coli*	Reduced 70% with 10 µg/ml in agar	Disruption of the cell membrane, Ag+ ions affect the DNA replication
Silver	13.5	*S. aureus*	Inhibitory concentration of 3.56µg/l respectively added to the agar surface and the population reduced up to 80%	Disruption of the cell membrane, Ag+ ions affect the DNA replication

Green synthesis of Zinc Oxide (ZnO) nanoparticle

Synthesis of the metallic nanoparticle by the using the green resources like plant extract is an eco-friendly, cost-effective, biocompatible and safer technique. Being a member of metal oxide nanoparticle, Zinc Oxide (ZnO) nanoparticle has been applied in different field like piezoelectric, optical, and magnetic gas sensing [45]. ZnO nanoparticle is an inorganic water-insoluble compound and seems like white powder. ZnO nanoparticle has great diversity with biomedical properties like antibacterial, and it used to disinfect wastewater and to disintegrate pesticides, herbicides [46]. It has been stated that the synthesis of ZnO nanoparticle has been done by various plant extract, known as green synthesis (table 5). Plant extracts contain some phytochemicals that performed like reducing and stabilizing factor in the reaction system. Phytochemicals are produced by the plant parts like root, stem, leaf, fruit, and seed because they can produce phytochemicals they are applied in the reaction mixture during the synthesis of ZnO nanoparticles.

Plants are the most promising source for the nanoparticle production because they conduct a higher amount of nanoparticle formation, with stable, modified size and shape. Green synthesis of ZnO nanoparticle require the target plant part like a leaf, flower, stem then the desired plant part should be washed properly in running tap water then sterilized in double distilled water. Then the desired plant part is kept in dry place for 10-15 days to make it dry. Then with the help of the domestic blender, dried plant part should be converted into powder. Then Milli-Q water should be added to the desired plant part and then boiled the mixture with continuous stirring by using a magnetic stirrer. Then the Whatman filter paper was used to purify the mixture and separate the desired solution which is needed for further experiments. The obtained extract should be mixed with Zinc Nitrate ($Zn(NO_3)_2$) or Zinc Sulphate ($ZnSO_4$) with the addition of NaOH and boiled at 30°-35°c for 1-4 hour. Reaction mixture changes its colour to yellow within the incubation time which visually confirms the formation of ZnO nanoparticles. The reaction mixture should be centrifuged to get the pellet followed by measuring the absorption maxima using UV visible spectrophotometer to confirm the formation of ZnO nanoparticle [47].

Table 5. A large number of plants are used to synthesize the ZnO nanoparticles are mentioned below [47-50].

Plants	Plants part	Size(nm)	Shape
Azadirachta indica	Leaf	18	Spherical
Agathosma betulina	Leaf	15.8	Quasi-spherical agglomerates
Aloe vera	Leaf	8-20	Spherical, oval, hexagonal
Anisochilus carnosus	Leaf	56.14	Hexagonal wurtzite, quasi-spherical
Calatropis gigantea	Leaf	30-35	Spherical shaped forming agglomerates
Cocus nucifera	Coconut water	20-80	Spherical and predominantly hexagonal without any agglomeration
Coptidis rhizoma	Dried rhizome	2.9-25.2	Spherical, rod shaped
Eichhornia crassipes	Leaf	32-36	Spherical without aggregation
Moringa oleifera	Leaf	24	Spherical and granular nanosized shape with a group of aggregates
Nephelium lappaceum L	Fruit peels	50.95	Needle-shaped forming agglomerate
Ocimum basilicum	Leaf	50	Hexagonal
Parthenium hysterophorus	Leaf	22-35	Spherical, hexagonal
Phyllanthus niruri	Leaf	25.61	Hexagonal wurtzite, quasi-spherical
Plectranthus amboinicus	Leaf	50-180	Rod shaped nanoparticle with agglomerates
Pongamia pinnata	Leaf	26	Spherical, hexagonal, nanorod
Rosa canina	Fruit extract	13.3	Spherical
Santalum album	Leaf	100	Nanorods
Sphathodea campanulata	Leaf	30-50	Spherical shaped forming agglomerates
Trifolium pratense	Flower	60-70	Spherical
Vitex negundo	Leaf	75-80	Spherical

Factors that are affecting the green synthesis of Zinc Oxide nanoparticle

Effect of pH

pH plays an important role in the unification of ZnO nanoparticle, the pH of the reaction mixture controls the size of the ZnO nanoparticle. For example, ZnO nanoparticle synthesized from *Sargassum myriocystum* extracts shows that the when the pH of the reaction mixture low (pH 5-7), accumulation of the ZnO nanoparticle occur to form larger particle, whereas in the high pH (pH 8) this accumulation does not occur, and it results in the complete reduction of Zinc Nitrate to Zinc Oxide in the reaction medium [48].

Effect of temperature and time

Temperature plays a crucial role in the green synthesis of ZnO nanoparticle when we use the green synthesis technology the required temperature for the reaction must be less than 100°c. For example, leaves extract of *Sargassum myriocystum* when used to synthesize the ZnO nanoparticles, the optimum temperature for this synthesis process is 80°c, within this temperature the absorption peaks were detected at 376 nm. At this temperature Zinc Nitrate which is present in the solution converts into Zinc Oxide nanoparticle. But when this reaction was performed in other temperatures like 50°c, 60°c, 70°c, 90°c, 100°c, there was no absorption peak at

376 nm [48]. Time plays a crucial role in the synthesis process. The incubation time of the reaction medium relies on the plant extract. For example, the incubation period for the green synthesis of ZnO nanoparticle from *Parthenium hysterophorus* leaves extract was 6 hours [49].

Influence of the reactant

Plant extract concentration in the reaction medium plays a crucial role in the formation of ZnO nanoparticles. For example, *Azadirachta indica* extract contains some functional group like ketone, alcohol, amine, a carboxylic acid which produces spherical shaped ZnO nanoparticles, whereas *Agathosma betulina* extract includes a hydroxyl group, which produces Quasi-spherical agglomerates [50, 51].

Antibacterial activity and other applications of Zinc Oxide nanoparticles

ZnO nanoparticle shows antibacterial activity by forming intercellular reaction oxygen species like Hydrogen peroxide (H_2O_2), which is lethal to bacterial cells. H_2O_2 which is produced by the Zinc Oxide nanoparticle, penetrate the bacterial cell through its membrane and kill them (table 6) [52-54]. In the development of several kinds of medicinal products, ZnO nanoparticles are governed due to its disinfecting, antibacterial, and drying properties. In the past ZnO nanoparticles were applied for the treatment of epilepsy and diarrhoea and administered orally [55-56]. ZnO nanoparticle can absorb the radiation like UV A and UV B, and now it is applied in sunscreens [57]. It also applied in the development of dermatological products against inflammation and itching. It also applied as a dusting powder and used treat wound. ZnO nanoparticles are also applied in the nutritional products and diet supplements, and it also applied in the dental paste [53].

As a pollutant removal and disinfectant, ZnO nanoparticle has been applied extensively because of their high chemical stability and oxidation-reduction capability. ZnO nanoparticles also applied in bioimaging technique, used in the biosensor technique and gene therapy technology [59]. Thermal conductivity property of ZnO nanoparticle makes it useful by the rubber manufacturing industry to construct various product in which ZnO nanoparticle act as a cross-linking agent with rubber. In the textile industry ZnO nanoparticle used as UV protective and air permeable agent [60].

Table 6. MIC of Zinc Oxide nanoparticle against pathogenic bacteria [58].

Nanoparticle	Size	Organism tested	MIC	Proposed mechanism
Zinc Oxide	13	*Staphylococcus aureus*	Reduced 95% of the bacterial growth at the concentration of 80 µg/ml	ROS inhibition
Zinc Oxide	60	*S. aureus*	Reduced 50% of the bacterial growth at the concentration of 400 µg/ml	ROS inhibition
Zinc Oxide	40	*S. aureus* *Escherichia coli*	Reduce the 99% growth of both species at 400 µg/ml	Membrane disruption
Zinc Oxide	12	*E. coli*	Reduced 90% at 400% µg/ml	Membrane damage due to particle abrasiveness

Conclusion

The particle which belongs to the nanoscale dimension has a big surface area to volume ratio, which makes them more specific and available. Nanoparticles which are metallic can be synthesized by using plant extract, in other words by the help of green synthesis technology we can synthesize metallic nanoparticles. Nanoparticles synthesized by green technology is eco-friendly, cause no pollution and less expensive. A crucial role is played by the plant extract in this synthesis process, and act as stabilizing, capping or hydrolytic agents. Silver (Ag) and Zinc Oxide (ZnO) are two metallic nanoparticles, and these two nanoparticles can be synthesized with the help of plant extract. There are numerous diverse plants are present those may be utilized for the creation of these two nanoparticles. Nanoparticles like Ag and ZnO have the antibacterial activities which are exploited to cure several diseases, caused by Multi-Drug Resistant (MDR) bacteria. These two particles have excessive potential to inhibit MDR bacteria.The MIC value of Ag NPs against *E. coli* and *S. aureus* were 70% and 80%. The applied concentration of Ag NP against *E. coli* was 10 µg/ml and for *S. aureus* was 3.56 µg/ml. Additionally, the MIC value of ZnO against *E. coli* and *S. aureus* was 99% and 95%. The applied concentration of ZnO NP was 400 µg/ml for both bacteria, and this value was much higher than Ag NP. From the above information, we can conclude that Ag NP is a more active antibacterial agent because it has a lower MIC value with respect to MIC value of ZnO NP; hence, Ag NP is more potent antibacterial agent than ZnO NP. Along with antibacterial properties, ZnO np can also utilize in other fields like the cosmetic industry, water purification industry, rubber industry etc.

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