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Role of medicinal plant in synthesis of green silver nanoparticles as antibacterial agent

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Abstract

In this current era, the fasten antibiotic-resistant of pathogens towards traditional antibiotics, has accountable for major global health problem. Researchers are perceptive to investigate for unconventional non antibiotic antimicrobial agents to control escalating development of bacterial resistance by microorganisms to antimicrobial drugs for prevention of infections caused by resistance pathogens. Different strategies with guiding principles are tested to build up effectual successive antibacterial agents, as widely used traditional physical and chemical methods for the production of NPs are high-cost with along with toxic byproducts, as well as harmful for the environment. In this admiration, green syntheses of nanoparticles are unquestionably promising materials, to reduce the use of hazards chemicals in development of nanoparticles by substituting them with plant-based materials. Silver nanoparticles (GAgNPs) have ability to go through the cell wall by penetrating the membrane of bacteria to amend their virulence potential by interaction with crucial biomolecules making trouble in molecular mechanisms. In fusion with suitable antibiotics, AgNPs may show synergistic effect and help to prevent the increasing worldwide bacterial resistance. Furthermore, due to unique characteristics such as superior biocompatibility and biodegradability GAgNPs have become the researcher's center of attention of new antibacterial materials due to their small particles, large surface to volume area, physical, mechanical and chemical properties. In this review, we investigated recent studies regarding the potential function of plant extract as a reducing/ capping /stabilizing agent and the antimicrobial activity of AgNPs, their potential for use in the medical and pharmaceutical field.

Keywords: Green synthesis, Green silver nanoparticles (GAgNPs), capping agent, Antibacterial activity, Nanoparticles (NPs)

Introduction

In the last century, one of the most essential medical achievements in the history of mankind was finding of antibiotics. In fighting against infectious pathogens the use of antibiotics are very frequent and successful armaments. Due to unawareness, increased in consumption of antimicrobial drugs, improper prescribing of anti-microbial therapy and excess use of many common antimicrobials agents may occur because the drug choice by physicians is based on a combination of low cost and low toxicity that trend responsible for creation of super-resistant bacteria in the body of host, which has seriously augmented the death rate of infected patients and constitutes a uncompromising warning to public health ^[1, 2]. As the size assortments in between 1-100 nm, physical and chemical properties of NPs have absolutely differed drastically from their parent metal. Although AgNPs can be synthesized by different physical and chemical routes, but green synthesis AgNPs is an environmental friendly phyto-chemistry approach which is non-toxic, biocompatible and inexpensive, as rational antibiotics have to achieve a single target so bacteria can easily develop self-resistant by enzymatic degradation, alteration of bacterial proteins and changes in membrane permeability ^[3].

The continuous intensification of multi-drug-resistant pathogens makes it imperative to build up new methods to muddle through with this global treatment challenge ^[4]. It is predictable projection that antimicrobial resistance may be accountable for approximately 10 million deaths per year by 2050, which will outnumber cancer deaths ^[5]. Search of a safe and successful antibacterial agent, has become researcher focus of attention. In order to solve the increasing serious problems in the post-antibiotic era, new strategies for the management of microbial infections are immediately needed ^[6]. Nanotechnology provides innovative type of antibacterial agent that brings novel opportunity for pharmaceutical applications by altering the physico-chemical characteristic of that particular substance. Several NPs that have been discovered in recent decades have promising therapeutic effectiveness against various life threatening pathogens, including antibiotic-resistant microorganisms.

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Nano-antibacterial material has advanced penetrating power due to exceptional physical and chemical properties, such as ultra-small size, large surface area to mass ratio. With the help of Nano technological developments, NPs that can be designed with desired properties have started to emerge as skilled tools [17].

As a whole metal NPs have gripped enormous attention as bactericidal agents with their sole properties. Various metal NPs including silver (Ag), copper (Cu), selenium (Se), nickel (Ni), gold (Au), zinc oxide (ZnO), titanium dioxide (TiO₂), and iron oxide (Fe₃O₄), have been extensively studied for their antimicrobial effects [18].

The size, surface area, morphology, net charge and physicochemical properties of NPs are the vital factors that modify their antimicrobial property through manifold mechanisms. While size of the NPs decreases, then surface-to-volume ratio increases a lot. More surface areas of NPs afford enhanced interface with microorganisms and to a great extent manipulate their antimicrobial activities. Among metal NPs, positively charged ones have been reported to bind more compactly to negatively charge bacterial surfaces and show superior antimicrobial effects. The spherical NPs have been shown to have a better antimicrobial effect as they allow more ions to be released due to their larger surface area [19]. For example Danielle Slomberg and her co-researcher evaluated the usefulness of (Nitric oxide) NO-releasing silica nanoparticles. According to their claimed smaller NO-releasing particles (14 nm) exhibited better NO delivery and enhanced bacteria killing ability compared to the larger (50 and 150 nm) particles, as well as rod-like NO-releasing nanoparticles proved more successful than spherical particles in delivering NO and inducing greater antibacterial destroyer throughout the biofilm [10]. Shiva K. Rastogi and co-researcher were studied on silver-silicon dioxide (Ag-SiO₂) hybrid and silver colloid (Ag-c) nanoparticles (NPs). Ag-SiO₂ and Ag-c NPs prepared by the cost-effective reduction method shows great promising antimicrobial activity against both gram-negative and gram-positive bacteria [11].

Nanoscience and Nanotechnology

Nanoscience is the study of phenomenon and exploitation of resources at minute and molecular levels, where properties are extremely different from those at larger scale [12]. Nanoscience is inter-disciplinary science which covers the areas of physics, chemistry, biology, and medicine [13].

Nanotechnology is defined as a science which deals with the synthesis, characterization, exploration and application of nano-sized materials for the development of science. This technique is new and modern for diagnosis and treatment of various human diseases or disorders [14, 15 & 16]. Nanotechnology, and alongside nano structured materials, play an ever increasing role in science, research, economy, every day's life, as more and more products based on nano structured materials are introduced to the market [17].

Nano biotechnology is an area that has emerged as a junction among biotechnology and nanotechnology for build up new biosynthetic devices and eco-friendly technology for the synthesis of nanomaterials [18].

Nanoparticles

The prefix nano is derived from Greek word nanos which meaning "dwarf" or very tiny [19]. Nano-sized materials acquire unique and enhanced properties because of their bigger surface area to volume ratio. Nanoparticles (NPs) can be mostly divided into two, namely, organic NPs and

inorganic NPs which comprise dignified metal NPs (like silver and gold), semi-conductor NPs (like titanium oxide and zinc oxide) [20].

Synthesis of Silver Nanoparticles

Silver Nanoparticles (AgNPs) can be prepared by an enormous variety of methods which usually are categorized in two main synthetic routes which are the top-down and the bottom-up approaches [21].

Top-down approach

In the top-down (physical) approach, AgNPs are acquired from their bulk materials using diverse methods and techniques like thermal decomposition, irradiation, laser ablation, arc discharge etc.

Bottom-up approach

In bottom-up (chemical and biological) approach, AgNPs are acquired from their essential building blocks which respond to generate AgNPs of the preferred shape and size.

Chemical approach

Commonly, chemical synthesis of AgNPs comprises the following three major components [22]: (i) metal precursors, (ii) reducing agents and (iii) stabilizing/capping agents. The problems associated with chemical methods are extensive use of toxic chemicals, non-ecofriendly nature of the process, need expensive chemicals with high energy input, requirement of sophisticated instrumentation and further lead to the presence of some toxic chemicals adsorbed on the surface that could produce intolerable toxicity to humans and adverse effects in biomedical applications [23].

Chemical method requires chemical reducing, capping and stabilizing agents which are mostly toxic, flammable, cannot be easily disposed of due to environmental issues, low material conversions, and high energy requirements [24]. The most commonly used organic and inorganic reducing agents are (sodium citrate, ascorbate, sodium borohydride, Tollens reagent etc.) for the reduction of Ag⁺ ions in aqueous solutions [25]. Capping agents play a very pivotal and versatile role in AgNPs synthesis. AgNPs can be functionalized and stabilized using capping agents to impart useful properties by controlling morphology, size and protecting the surface thereby preventing aggregation.

Green synthesis of silver nanoparticles

Green synthesis is a new and sophisticated process which requires biogenic matter including plant extracts, biopolymers and microbial sources like bacteria, fungi, algae, and yeast for nanomaterials production. Improvement of biocompatible, non-toxic and eco-friendly methods for the synthesis of AgNPs is a matter of concern in green chemistry [26].

The development of green synthesis of AgNPs is succeeding as a key branch of nanotechnology; where the use of biological entities like micro-organisms, plant extract or plant biomass for the manufacture of AgNPs could be an alternative to chemical and physical methods in an eco-friendly manner [27]. For biological synthesis of AgNPs the reducing agent for reducing Ag⁺ ions and the stabilizing agents for reducing the aggregation of AgNPs are changed by molecules formed by living organisms. In case of green synthesis of AgNPs having the following advantages over traditional chemical methods. (i) Green synthesis is easy and usually involves a one-pot reaction; (ii) it is amenable to scale up; (iii) the toxicity connected with harmful chemicals are removed, (iv) green

biological entities can be used as reducing and capping agents, and (v) finally, the method is cost expensive, need little intervention or input of energy, uses renewable source, environmental friendly technique and it is not compulsory to use high pressure, energy, temperature and poisonous chemicals [28].

Plant extract as a capping agent

The capping agents used to modifying nanoparticles which were selected on the basis of their prominent biological properties like bio-compatibility, bio-degradability, bio-availability, and bio-solubility so that the applicability of such capped nano material should be superior in the living cellular atmosphere. The small-sized nanoparticles can easily float in the human body in comparison to their larger particles, therefore preferred and chosen for nano-medical purposes. A suitable selection of capping agents is necessary to control the constancy, stability and functionalization of the synthesis of nanoparticles. The capping agents used for maintaining size, shape, aggregation, and physico-chemical properties in the synthesis of nanoparticles [29].

Chemical capping agents are rough to separate from the surface of the nano particles and are non-biodegradable. Thus, there may be an urgent want to go looking and searching for green capping agents in order to secure the biological system. Observe this scenario, Researchers nowadays is concentrating modern green synthesis by using naturally occurring Plant extract as a reducing, stabilizing and capping agent [30].

Different crude parts of plants, including the fruits, flowers, seeds, buds, leaves, stem, root, rhizomes, callus, bark and latex, have been widely utilized in the green synthesis of nanoparticles due to the existence of various bio-molecules. The plant-based phyto-constituents like polyols, alkaloids, polysaccharides, steroids, saponin, tannins, terpenoids, flavonoids, phenolics, proteins, amino acids, enzymes, and vitamins function as strong chelating, reducing, and stabilizing agents, which provide stability, prevent

agglomeration, and help in fine-tuning the shape and size of the nanoparticles [31]. Plants have get massive significance in the field of nano science due to their cost-effectiveness, nontoxic, easy availability, and non infectious, along with economic prospective includes mild circumstances for biosynthesis, large-scale production, and an extensive range of biological activities [32].

Role of secondary metabolites

Various literature studies showed that secondary metabolites play a key role in the reduction of metal ions and redox reactions for the formation of a nano sized mass of metal oxide nanoparticles. For example, Sreenivasa Nayak and his co researcher reported the synthesis of silver nanoparticles by using *Dillenia indica* L. leaf extract. In this study, FTIR showed the various peaks of spectral data at 541, 668, 778, 862, 1044, 1119, 1266, 1318, 1384, 1427, 1459, 1597, 2853, 2923, and 3416 cm^{-1} . The peaks at 3416, cm^{-1} stand up an association of free -COOH groups, as well as 1597 cm^{-1} recognized sharp peak in the stretching modes of nitro, containing oxygen molecules, and functional groups of esters contributed the peak at 668, 778 and 862 cm^{-1} . These stretching vibrational peaks clearly indicate the presence of bio-molecules as stabilizing agents. TEM results express that GAgNPs were spherical in shape with size in the range of 10.01-23.24 nm. Furthermore, zeta potential study shows evidences that external parts of nanoparticles were negatively charged with a sharp peak at -39.5 mV zeta potential. This negative charge is liable for repulsion amongst the synthesized nanoparticles, resulting stability of GAgNPs for a long time. In this study of phytochemical transmission carry out by Researchers confirm the presence of secondary metabolites that play a multifunctional role of a weak base source, as well as oxidizing, capping, and chelating agents without the addition of any base chemical reagent in the preparation of nanoparticles [33].

Table 1: Antibacterial activity of green silver nanoparticles (GAgNPs)

SL. No	Plant extract used as Capping Agent	GAgNP Size & Shape	Antibacterial activity	Researcher	Reference
1	Acorus calamus extract	31.83	Antibacterial activity against <i>Bacillus subtilis</i> , <i>Bacillus cereus</i> , and <i>S. aureus</i>	JR Nakkala, R Mata, Arvind Ku Gupta, Sudha Rani Sadras	[34]
2	Acacia cyanophylla plant extract	88.11	Antimicrobial activity against <i>E. coli</i> isolates	JoudJalab, AdawiaKitaz	[35]
3	Brassica oleracea extract	20	The antibacterial activity against <i>Staphylococcus epidermidis</i> (Gram positive) and <i>Pseudomonas aeruginosa</i> (Gram negative)	Sabah Ansar, Hajera Tabassum, Norah SM, Aladwan and <i>et al.</i>	[36]
4	Boerhaaviadiffusa extract	30-40	Predominant antibacterial activity against <i>Pseudomonas aeruginosa</i> and <i>K. pneumonia</i>	Sunday Adewale Akintelu <i>et al.</i>	[37]
5	Cassia tora L aq. root extract	20,50,100	<i>P. seudomonas</i> and <i>S. aureus</i> were highly sensitive to the synthesized silver nanoparticles	Rahimullah Shaikh Imran Zainuddin Syed, Payoshni Bhende	[38]
6	Cassia roxburghii extract	15-20	Antibacterial activity against (<i>S.aureus</i> and <i>B.cereus</i>)and Gram-negative (<i>E. coli</i> and <i>P. aeruginosa</i>)	Pooja Moteriya, Hemali Padalia, Sumitra Chanda	[39]
7	Root Extracts of <i>Rubus ellipticus</i> Sm.	13.85-34.30 nm	Antibacterial activity against <i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> and <i>Klebsiella pneumoniae</i> .	Lekha Nath Khanal, Khaga Raj Sharma <i>et al.</i>	[40]
8	<i>Cymbopogon citrates</i> extract	47nm	Antibacterial effect against <i>S Paratyphi</i> , <i>B. cereus</i> and <i>S. Flexneri</i> . <i>E. coli</i> and <i>V. Cholerae</i>	S M Rakib-Uz-Zaman Kashmery Khan ;Sadrina Afrin Mowna <i>et al.</i>	[41]
9	<i>Eulophia herbacea</i> Lindl tuber aqueous extract	11.70 ± 2.43nm	Antibacterial activity against Gram-positive bacteria (<i>S. aureus</i> , <i>B. subtilis</i>) and Gram-negative bacteria (<i>E coli</i> , <i>P aeuroginosa</i>)	Jayashri S. Pawar & Ravindra H. Patil	[42]
10	<i>Aaronsohnia factorovskyi</i> leaf extract	104-140 nm	Antibacterial activity against <i>Staphylococcus aureus</i>	Fatimah Al-Otibi, Reem A. Al-Ahaidib <i>et al.</i>	[43]
11	<i>Garcinia mangostana</i> extract	15-20	Antibacterial and antioxidant activity action against <i>E. coli</i> and <i>S. aureus</i>	Perumal Karthiga	[44]
12	<i>Lantana camara</i> extract	86 nm	Antibacterial and antioxidant activity action against <i>E. coli</i> and <i>S. aureus</i>	Narahari Narayan Palei, S. Ramu,	[45]

13	<i>Cannabis sativa</i> Leaf Extracts	15-20 nm	antibacterial activity against several human pathogens: <i>Escherichia coli</i> , <i>K. pneumoniae</i> , <i>Pseudomonas fluorescens</i> , and <i>Staphylococcus aureus</i> .	Adriana Cecilia Csakvari, <i>et al.</i>	[46]
14	Musa paradisiacal peel extract	42-67nm	antibacterial activity against <i>B. subtilis</i> , <i>E. coli</i> , and <i>S. aureus</i>	Haytham.M.M. Ibrahim	[47]
15	<i>Tinospora cordifolia</i> leaf extract	8-74 nm	antibacterial efficacy against <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i>	S.Rachel Deva Kirubai & , M.M. Abdul	[48]
16	<i>Leptadenia reticulata</i> leaf extract	spherical shape 50-70 nm.	Better antibacterial activity <i>E. coli</i> ; <i>B. subtilis</i>	Kumara Swamy M, Sudipta, KM, Jayanta K, <i>et al.</i>	[49]

Mechanism of antibacterial properties of Green silver nanoparticles (GAgNPs)

Along with all of the metals nanoparticles which are considered as antibacterial agents, GAgNPs have been proven to be the most effective for a wide range of bactericides [50]. These particles have the capability to destroy the microbial growth in human body [51]. The bactericidal efficiency of GAgNPs mainly depends on their size and shape, smaller size GAgNPs are more effective as compared with the larger one, in addition to, the quantity of GAgNPs is directly proportional to their antimicrobial effect. The antimicrobial action of smaller size of G AgNPs will be better due to higher affinity with enlarge surface area make them easy to penetrate towards microbial cell wall [52]. The highest concentration of released Ag⁺ was observed in the case of GAgNPs with the maximum surface area resulting in strong bactericidal efficiency. Similarly the lowest concentration of Ag⁺ released was noted for GAgNPs with the lowest surface area, resulting in weak bactericidal efficiency [53].

Antibacterial mechanisms of GAgNPs through

(i) Bacterial cell penetration through coulombs attraction

Cellular structure of bacteria composed of lipopolysaccharides has a negative charge due to the presence of carboxyl, phosphate, and amino groups [54]. The positive charge GAgNPs confers Coulomb interaction between GAgNPs and negatively charge cell surface of the bacteria, thereby GAgNPs get in touch to the bacterial cell, break cell membrane permeability and respiration, As a result of this battle shrinkage of the bacterial cytoplasm, detachment of membrane, formation of multiple electron-dense pits, which cause the release of lipopolysaccharide molecules and membrane proteins and lipids and DNA, eventually membrane disruption, which can lead to bacterial death [55].

(ii) Cause toxicity by the release of Ag⁺ from the surface of GAgNPs.

GAgNPs have more exceptional physicochemical and biological properties ahead of parent silver [56]. In aqueous solutions GAgNPs can be chemically oxidized to give (Ag⁺) metallic ions. From the surface of GAgNPs the released ions have an essential function in antibacterial action. Due to their nano in size, easily penetrate and pass through the cell wall and interact with the cell membrane [57]. It was also established that the antibacterial effect of GAgNPs on Gram-negative bacteria was stronger than Gram-positive bacteria as the cell wall thickness between Gram positive bacteria (30nm) and Gram-negative bacteria.

(3-4 nm) [58, 59]. Consequently, enhanced antibacterial effects can be obtained by altering the surface charge of GAgNPs to

achieve stronger attractive force. GAgNPs can sustainably release Ag⁺ in and out of bacteria, GAgNPs interaction with ribosomes lead to their denaturation causing inhibition of translation and protein synthesis inhibit intra-cellular biological functions, and lead cell death [60].

(iii) Produce oxidative stress by generating reactive oxygen species (ROS)

Natural antioxidative defense systems maintain by bacteria to deal with oxidative stress. Natural antioxidants carotenes and ascorbic acid are the examples which prevent lipid peroxidation or other ROS-related stresses. Additionally, they have some important enzymes like catalase, peroxidase, and superoxide dismutase that transfer into toxic reactive oxygen forms into non-toxic or less toxic forms. On the other hand, upon exposure to NPs, the addition of ROS exceeds a definite level and bacteria cannot handle with detrimental changes in critical cellular structures such as cell wall, cell membrane, DNA, and protein [61].

After that, chemically extremely generative ROS accumulation and ROS-induced oxidative spoil to chromosomal DNA and proteins, and finally cell stress in the bacterial cell cause induced aperture formation and lipid peroxidation in the cell membrane death. Another fundamental mechanism of the antibacterial effect of the NPs is the burst of ROS in the bacterial cell [62]. ROS are generated during the normal oxygen metabolism and are vital for diverse cellular signaling pathways. Oxygen acts as the ultimate acceptor of electrons transported by ETS during oxidative phosphorylation and is reduced to the water molecule. Some of these electrons are taken by molecular oxygen, resulting in the formation of O² that can then be transformed into H₂O₂ and OH. However, when bacterial cells are exposed to NPs, metal ions released from the surface of NPs induce ROS bursts by disrupting respiratory systems and can considerably increase intracellular ROS production [63]. Released metal ions contribute to further increase in intracellular ROS accumulation by causing disruption of membrane integrity, inactivation of cellular enzymes, disruption of the electron transport system, and decreased membrane potentials. GAgNPs can down regulate the production of bacterial antioxidant enzyme such as glutathione (GSH), super oxide dismutase, and catalase, which can speed up the gathering of ROS. Increased the level of ROS bring about an apoptosis-like reaction, lipid peroxidation, depletion of GSH, and DNA damage. In addition, the antibacterial activity of AgNPs was also influenced by adenosine triphosphate (ATP) associated metabolism and ROS [64].

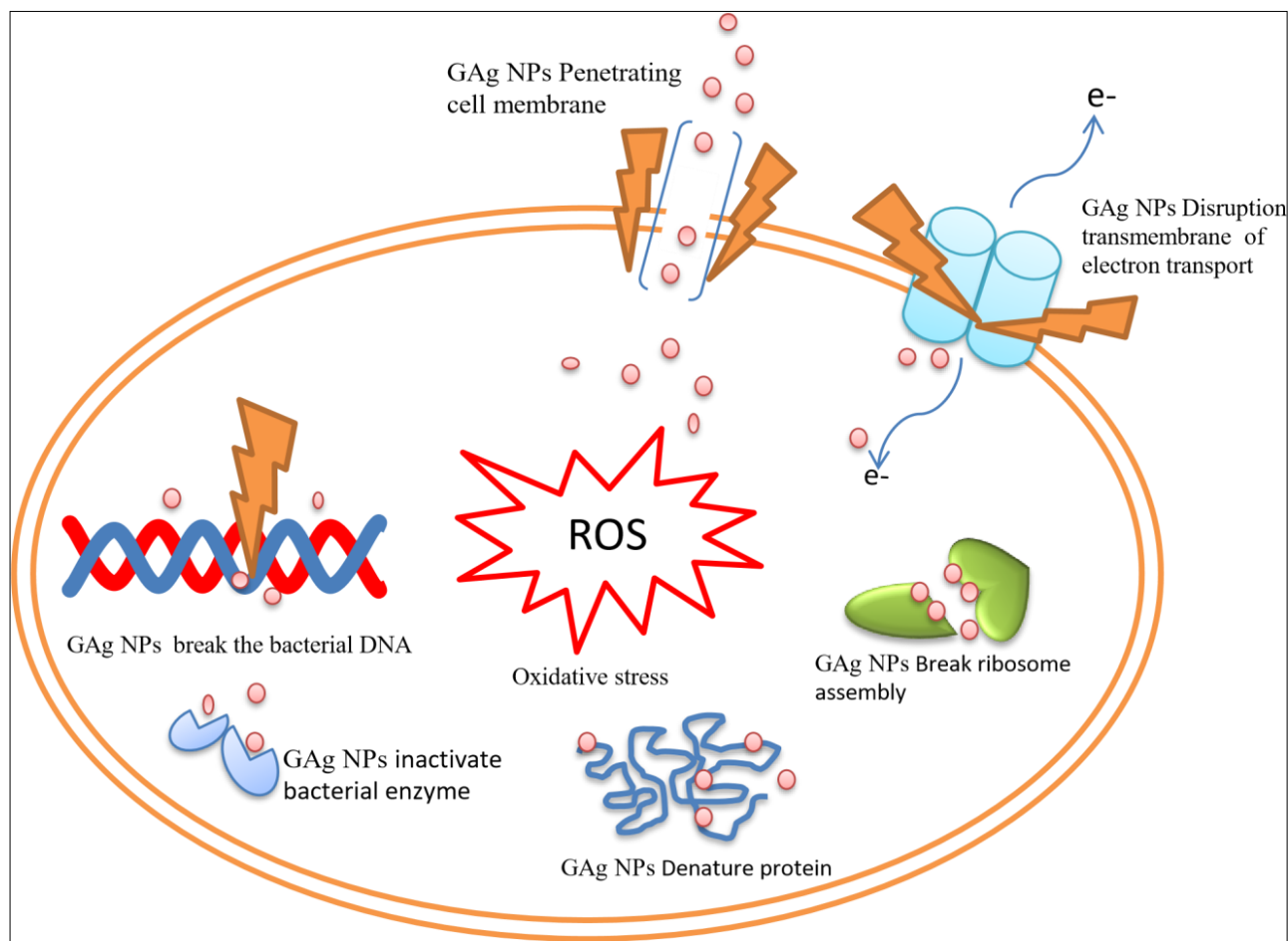


Fig 1: Antibacterial activity of green silver nanoparticles

Conclusion

The Green synthesis of silver nanoparticles, specially using plant extracts provides a natural, economical, nontoxic, rapid synthesis of silver nanoparticles. The synthesized silver nanoparticles with medicinal plant extract which reduce silver ions and stabilize the silver nanoparticles. It has been reported that medicinal plants are a rich source of phenolic compounds such as flavonoids and phenolic acids, etc. Additionally, plant organs contain different contents of phenolic compounds, therefore root, buds, bark, leaf, fruit, flower, stem, and the whole plant were chosen for the Green synthesis of silver nanoparticles studies. Silver nanoparticles demonstrate enormous guarantee as antimicrobial agents. While the antimicrobial properties of silver have been recognized for ages, the advent of nanotechnology can help to develop this extraordinarily asset for mankind. GAgNPs, if administered properly, can be more precise and make sure targeted delivery to the affected area. The usage of silver nanoparticles also has the considerable prospective to assist and work out the rising emergency of microbial resistance due to their non-specific binding mechanisms. That is, metal nanoparticles like GAgNPs do not bind to a particular site within the bacterial cell, thereby dropping or negligible the probability of building microbial resistance. It is, for that reason, Green synthesized nanoparticles could modernize drug delivery. For the production of nanoparticles the last decades have witnessed the application of chemical and physical methods of synthesis. As the conventional methods of synthesizing silver nanoparticles have harmful effects on the environment and human health, to overcome their difficulty of antimicrobial resistance without worsening the problem of climate change and global warming, industries need to accept

Green and sustainable methods of synthesis. Biological methods, with use plants extract as renewable sources, are potential alternatives. They also produce silver nanoparticles with effective antimicrobial properties against bacteria. though, the majority of the research on Green methods is still at a small scale and required to be scaled up for industrial applications. Other additional aspects, such as drug release techniques, also need to be improved to reduce the possible toxicity of silver nanoparticles. For that reason, it is essential to sponsor and support the Green synthesis of silver nanoparticles research in pharmaceutical academics, industries and research laboratories.

Conflict of interest:

Authors declare that there is no conflict of interest.

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