Green Synthesis of Silver Nanoparticles using Plant Extracts and Their Applications for Water Purification and Anti-Diabetic Properties

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Abstract

The study reports the synthesis of silver nanoparticles (AgNPs) using green method where plant extracts of Turmeric, curry-leaves, Ashwagandha, Arjun, Aloe vera and Tulsi were used as reducing agents. Characterization was done using UV-Visible spectroscopy and Scanning electron microscopy. UV-Visible spectrum showed peak absorbance around 420nm and SEM-EDAX analysis confirmed the presence of AgNPs in a size range of 50-80nm. Ability of the synthesized AgNPs as an antimicrobial agent was studied and their use was extended to the treatment of contaminated water.

It was found that 30µL of AgNPs effectively decontaminated water containing 10^3 CFU/mL E. coli within 10 minutes. The study also focuses on the effect of the nanoparticles on the growth of Saccharomyces cerevisiae as a model organism for eukaryotic cells. No significant effect on the growth of S. cerevisiae was observed. Effect of AgNPs on advanced glycation end-products (AGEs) was also studied. AGEs are formed due to non-enzymatic glycation in hyperglycemic conditions leading to secondary complications in diabetes. AgNPs synthesized using Ashwagandha, curry-leaves and Aloe vera showed anti-glycating properties in a concentration dependent manner. This suggests that these properties of AgNPs may be used in many environmental and therapeutic applications but their use should be regulated and studied in detail.

Keywords: Silver nanoparticles, Characterization, Antimicrobial properties, AGEs, Antiglycation, Anti-Diabetic agents.

Introduction

The field of nanotechnology in applied science uses the unique properties of nanomaterial by controlling their size, shape and thereby altering their surface area to form different materials of size in nanometers. Nanoparticles (NPs) are materials that have all dimensions within 1-100 nm as defined by ISO[5].

Metal nanoparticles have been widely explored in the fields of material science and medicine. Interestingly, metal nanomaterial has found their way in electronics and new various other material designs of everyday use with rapidly growing use in medical research to develop targeted drug delivery, rapid detection tests, advance biomolecular sensing and as anti-cancer agents in cancer therapies. It has also been used to develop antivirals in addition to acting as anti-fungal and antibacterial agents[9].

This study focuses on the synthesis of silver metal nanoparticles (AgNPs). Due to their small diameter and large surface area to volume ratio, nanoparticles have altered physical, chemical, magnetic and optical properties compared to their bulk material, which has brought much attention to the nanoparticles in various industries. Silver for centuries has been used in cooking to make silverware utensils to store water without contamination and to prevent food spoilage. Hence it is also the most studied metal for exploring its various properties. In nanotechnology too, silver nanoparticles have widely been explored mainly for their antimicrobial properties. The Ag+ ions are believed to inactivate the respiratory enzymes, electron transport chain components and interfere with DNA functions[13]. Silver, in small amounts, is non-toxic to humans and shows a broad-spectrum antimicrobial activity. Silver nanoparticles are shown to be very effective and advantageous as an enhanced antimicrobial activity is seen by the continuous release of Ag+ ions[6].

There are many techniques or methods for the synthesis of silver nanoparticles, the easiest being chemical synthesis using a reducing agent to reduce the silver salt into silver atom aggregates. The choice of reagents should be such that it is renewable; the reagent should be biocompatible and should have highly reduced or no toxicity. The synthesis procedure should utilize minimum energy for the production of nanoparticles. The reagent itself should be safe to dispose of and easily recyclable. It should also generate minimum or no by-products during the synthesis procedure. Therefore, it is crucial to consider the usage of least toxic or no chemicals; or generating no toxic by-products that can in any way harm the environment when producing nanoparticles.

Hence green synthesis of nanoparticles as a part of the green approach is being explored widely and is the subject of the present research. The reagents chosen should be renewable, biocompatible and have low toxicity. Minimum energy should be utilized in the production and minimum or no harmful by-products that could harm the environment or humans should be generated in the production of nanoparticles[2].

Green synthesis of AgNPs using biological sources as reducing agent is therefore widely adopted as it is cost-effective, the raw materials are easily available and less toxic having ease of synthesis and absence of chemical agents[19]. Production of NPs using plant extract is rapid compared to bacteria and fungi being eco-friendly, economical, non-toxic and a one-step process[22]. This was first studied using Alfalfa sprouts[10], which had the ability to take up silver ions from agar using its root and pass it on to the shoot in the same oxidation state where the ions aggregated to form nanoparticles.

The main principle of green synthesis of a metal nanoparticle is to reduce the metal salt into its metal ions using water, heat, or changing the pH. The metal ion, using a biological source like plant, bacteria, fungi and algae extracts as a reducing or oxidizing agent, is reduced to its neutral metal atom, which then grows and forms an aggregate, which when stabilized or capped forms a nanoparticle of that metal[11]. The easiest way to characterize is using UV-visible absorption spectroscopy with an intense absorbance peak (Surface Plasmon resonance peak) in the range 410-440nm, confirming the successful formation of AgNPs[24]. Furthermore, the distribution of size is an essential factor and can be studied using Transmission electron microscopy (TEM) or Scanning electron microscopy (SEM).

Antimicrobial, antivirals, anticancer and antioxidative properties of silver nanoparticles have been widely studied. The application of AgNPs as therapeutics to treat several diseases is being explored. Recently, academic research has focused on exploring the potential of AgNPs in inhibiting the formation of advanced glycation end products (AGEs) leading to secondary complications of diabetes.

Diabetes leads to prolonged accumulation of glucose in the body which is extremely common in the human population. The carbonyl group of these sugars covalently binds to the amino groups of proteins, nucleic acids and lipids without the need for an enzyme. This non-enzymatic interaction between sugar and proteins leads to the formation of advanced glycation end products (AGEs)[16]. Therefore, AGEs are formed as a result of the Maillard reaction, also called glycation. Another significant property observed of the silver nanoparticle, was its inhibitory effect on AGEs[3]. Dicarbonyl compounds (Glyoxal, methylglyoxal etc.) are formed from the non-oxidative cleavage that readily reacts with amino acids to form AGEs. Food (soy sauce) and beverages (coffee, beer) and even cigarette smoke are found to have methylglyoxal (MG) and can increase type I diabetes by 5-6 folds and type-II diabetes by 2-3 folds in patients.

Excessive production and accumulation of AGEs are observed in hyperglycemic conditions and can lead to secondary complication of diabetes like atherosclerosis, retinopathy, neuropathy, cardiomyopathy, cataract and nephropathy; and ageing as well neurodegenerative disorders. Silver, gold and selenium nanoparticles are commonly used as anti-glycating agents. Nanoparticles are proposed to act by competitively binding to the amino groups of proteins and prevent the non-enzymatic interaction between the reducing sugar and the proteins. They have also been observed to have a high scavenging activity on ROS and an inhibitory effect on α-dicarbonyl compounds, which act as precursors for AGEs.

Natural inhibitors or antiglycation agents like medicinal herbs and dietary plants lack dose-dependent standardization for their safety and efficacy. Synthetic drugs used as antiglycation agents are known to cause liver and kidney toxicity, gastrointestinal disturbances, weakness, fatigue, shortness of breath, lactic acidosis, development of hypoglycemia etc. The glycation products are measured using several methods including the measurement of browning, total AGEs by spectrofluorimetry, fructosamines, carbonyl content, HPLC, protein structural characterization by CD and gel electrophoresis[12].

In this study, plant extracts from *Curcuma longa* (Turmeric)[18], *Ocimum tenuiflorum* (Tulsi)[7], *Withania somnifera* (Ashwagandha)[4], *Terminalia arjuna* (Arjun)[23], *Murraya koenigii* (Curry Leaves)[8] *and Aloe vera*[17] were used as a reducing agent for the synthesis of silver nanoparticles. The synthesized AgNPs were characterized; their antimicrobial activity and their effect on the growth of *S. cerevisiae* were studied. Further, this property was used to find its application in the treatment of water contaminated with *E. coli*. The synthesized silver nanoparticles were also used to study its inhibitory effects on AGEs.

Material and Methods

Collection of plant specimens: The collection of plant materials was done in accordance with the relevant national and international guidelines. None of the selected plants species is endangered or taken from wild and all are grown all over India. They are readily available for use in the local Indian markets. They are used regularly in everyday life as ingredients for cooking in Indian Cuisine.

Preparation of leaf extract: Turmeric, Curry leaves, Ashwagandha, Arjun, *Aloe vera* and Tulsi plants were chosen due to their known antimicrobial, anti-inflammatory, anti-oxidant and medicinal properties. They are also easily available and cheap, have high polyphenolic content and therefore act as good reducing agents[4,7,8,17,18,23]. The plants/parts that were locally available namely Turmeric (root), Ashwagandha, Arjun and Tulsi leaves were dried, powdered and used to prepare a 0.1% extract in distilled water. On the other hand, 10g Curry leaves and *Aloe Vera* plant leaves were washed with tap water and then with distilled water, air-dried and chopped finely. 10% extract was prepared by boiling 10g finely chopped curry leaves in 100ml-distilled water for 20mins. It was centrifuged at 12,000rpm/4^{o}C/15mins; the supernatant was collected and stored at 4^{o}C to be used as a reducing agent[3].

Synthesis of Silver Nanoparticles (AgNP): Chemical method was used to synthesize AgNPs to compare their efficacy against green synthesized nanoparticles and was also used as a control in all the experiments. Tri-sodium citrate (0.1%) that acts as a reducing agent was added drop wise to boiling colourless solution of 50ml of 1mM $AgNO_3$. The addition of tri-sodium citrate was stopped when the colourless solution turned permanent yellow.

Prepared plant extracts were used as reducing agents and were added drop wise to boiling colourless solution of 50ml of 1mM $AgNO_3$ till colour change was observed from colourless to pale yellow-brown. The final solution was centrifuged at 4000rpm/30 mins/24^{o}C and the supernatant was collected and stored at room temperature for a week before characterization.

Characterization of silver nanoparticles: Characterization of the synthesized silver nanoparticles was carried out using a UV-visible Spectrophotometer by measuring absorption spectra in the range 300-600nm. Distilled water was used as blank. The maximum absorption for silver nanoparticles lies between 410-440nm which is its unique characteristic property[1,24]. SEM-EDAX analysis was carried out to confirm the size and composition of the synthesized AgNPs.

Antimicrobial Activity of the synthesized AgNPs

Agar Cup diffusion method*:* Agar cup method was used to determine the antibacterial activity of the synthesized AgNPs using various plant extracts against *Escherichia coli* and *Staphylococcus aureus*. Filtered sterilized 30µl of the AgNPs were added to the well. 30µl distilled water was used as the negative control; 30µl of 50µg/mL ampicillin and 30µl of chemically synthesized AgNPs were used as the positive control. The AgNPs were allowed to diffuse as the plates were incubated at 37^{o}C for 24hrs. The diameter of the zone of inhibition was measured in millimeters[25].

Effect of AgNPs on *E. coli, S. aureus* and *S. cerevisiae:*
Sterile 5mL nutrient broth (for *E.coli* & *S. aureus)* tubes and YPD broth (for *S. cerevisiae)* were inoculated with 50µl of the actively growing culture. Synthesized AgNPs were added to each tube in increasing volume from 10µl to 500µl and incubated at 37^{o}C/24hrs for *E.coli* and *S. aureus and* at 23^{o}C/48hrs (optimum incubation time for the strain) for *S. cerevisiae* The O.D was determined at 600nm using a spectrophotometer post-incubation. Uninoculated media broth was used as a negative control and media broth inoculated with just the culture and without AgNPs was used as a positive control for growth.

Water Treatment using AgNPs: The Turmeric, Curry leaves and AgNPs, based on their antimicrobial properties were used in the treatment of contaminated water as an environmental application. These green AgNPs, along with chemically synthesized AgNPs (10µl each), were added to water containing 10^3CFU/ml *E. coli* (Treated) and incubated for 0 mins, 10 mins, 20 mins, 30 mins and 60 mins. 0.1mL of the treated water from each tube was spread on sterile nutrient agar plates using the spread plate technique and incubated at 37^{o}C overnight. The colony-forming units (CFU) were counted and viability was determined.

AgNPs synthesized using Arjun and Ashwagandha plant extracts were added to water containing 10^3CFU/ml of *E. coli* (Treated) at increasing volumes of 5µl, 10µl and 30µl. 50µl from the AgNPs inoculated treated tubes and then added to 5mL sterile nutrient broth after 0 minutes. The tubes were then incubated at 37^{o}C/24h and absorbance was measured at 600nm. 50µg/mL ampicillin was used as a positive control.

Effect of AgNPs on Advanced glycation end products:
Methylglyoxal (MG) is a sugar substitute found in many foods and beverages and acts as a glycating agent to BSA. AgNP inhibits the formation of advanced glycation end products in the reaction mixture. 3mg BSA and 6mM MG concentrations were used to carry out the reaction. 3mM sodium azide was added to prevent the growth of microorganisms. BSA without AgNPs and MG was used as control. Multiple blanks were prepared.

The reaction mixture was prepared in 0.05M phosphate buffer of pH 7.4. AgNPs were added in increasing volumes (50µl, 100µl, 200µl) to the reaction mixture. The total reaction volume was maintained at 1mL. The tubes were incubated for 7 days in a water bath maintained at 37^{o}C. After incubation, the absorbance was determined at 420nm using UV-Vis Spectrophotometer to confirm browning[10].

Results and Discussion

Synthesis and characterization of Silver Nanoparticles:
Silver nanoparticles were best synthesized chemically by adding 0.1% tri-sodium citrate to reduce 1mM $AgNO_3$ to silver atoms indicated by a change in the colourless solution to yellow. This was confirmed by measuring the absorption spectrum in the range of 300-600nm. Absorption maxima were observed at 420nm confirming the presence of silver nanoparticle.

Silver nanoparticles show characteristic absorption maxima at 420nm, a deviation from these maxima, either decrease (Blue shift) or increase (Red shift) in the absorption indicates the presence of impurities. Impurity, in this case, could be the components of the biological extract or the capping and stabilizing agents present inherently. Silver nanoparticles synthesized using various plant sources as reducing agents showed a peak wavelength around 420nm and were stable for over one year (Table 1).

The size of the synthesized AgNPs was confirmed using SEM analysis and showed an average size ranging from 50-80nm. EDAX analysis confirmed the presence of silver metal and no other metal impurities were detected.

Antibacterial effect of synthesized AgNPs

Antimicrobial activity of chemically v/s green synthesized AgNPs against *E. coli* and *S. aureus* using Agar Cup Method (Bioassay): Bioassay technique was used to determine the antibacterial activity of the synthesized nanoparticles against *E.coli* and *S.aureus*. It was observed that the AgNPs synthesized using plant extracts showed a zone of clearance around the well, comparable to the chemically synthesized AgNPs and ampicillin. The zone of inhibition diameter was larger in *E. coli* (Figure 1a) than that of *S. aureus* (Figure 1b). Distilled water used as a negative control showed no zone of clearance around the well. The average diameter zone of inhibition was found to be more against *E.coli* as compared to that against *S. aureus*.

This shows that AgNPs have better activity against gram-negative organism as compared to the gram-positive organism, this can be attributed to the thick peptidoglycan cell wall layer in gram-positive organisms which make it harder for the nanoparticles to penetrate the cell.

Table 1
Absorption maxima of synthesized AgNPs

Source	Scientific names	Λ max (nm)
0.1% Turmeric	*Curcuma longa*	421.0
0.1% Tulsi	*Ocimum tenuiflorum*	424.5
0.1% Ashwagandha	*Withania somnifera*	412.0
0.1% Arjun	*Terminalia arjuna*	421.0
10% curry leaves	*Murraya koenigii*	411.0
10% *Aloe vera*	*Aloe vera*	437.0
Chemical synthesis (control)	1% Tri sodium citrate	420.0

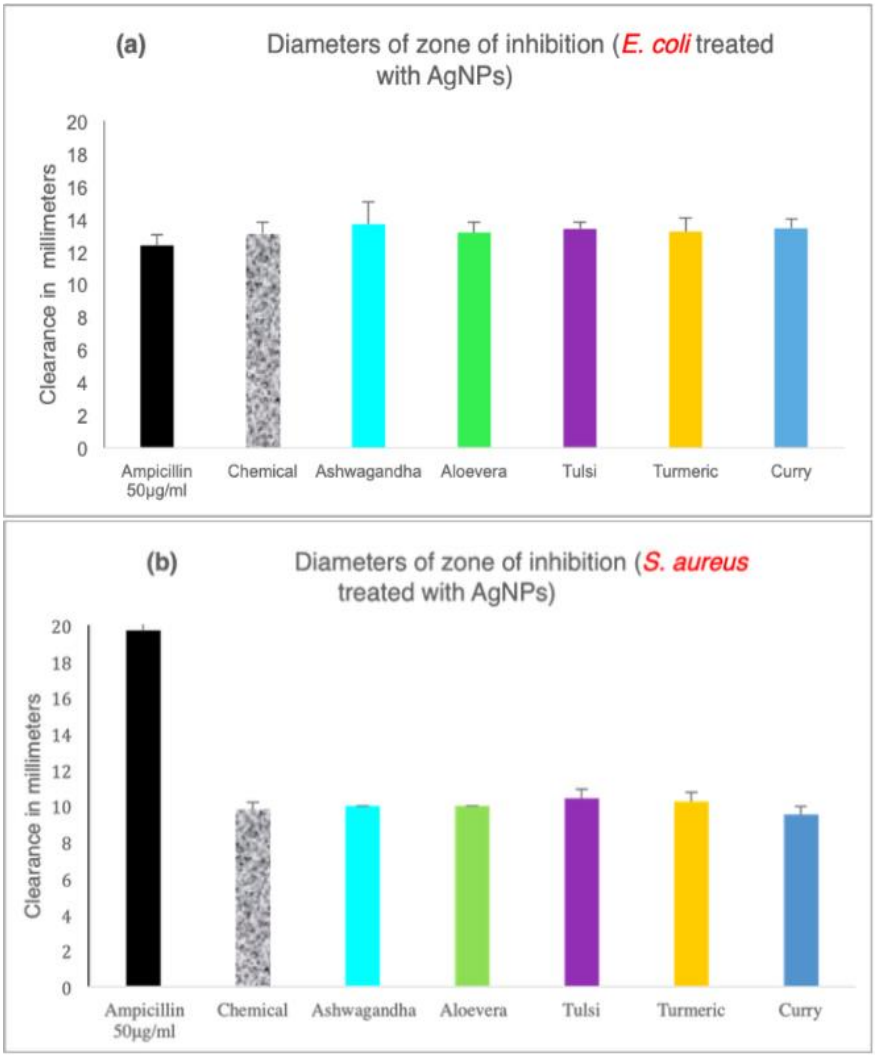

Figure 1: Diameter of zone of inhibition formed by ampicillin, chemically synthesized AgNPs and AgNPs synthesized using various plant extracts as given in the figure, on nutrient agar seeded with a) *E. coli* and b) *S. aureus*

Between chemically synthesized nanoparticles and green synthesized NPs, the green synthesized NPs showed a larger diameter against both *E. coli* and *S. aureus* which shows that green synthesized nanoparticles have better antibacterial activity as compared to chemically synthesized AgNPs. However, this difference is not too significant. A more systematic study should be carried out to determine the exact concentration and antibacterial activity against other model organisms.

Determination of the effect of AgNPs on the growth of *E. coli, S. aureus and S. cerevisiae*: Silver NPs synthesized using Turmeric, Arjun, Ashwagandha and curry plant extracts were observed to inhibit the growth of *E.coli* successfully as shown in fig. 2a. It was observed that even as low as 50µL of AgNP showed a decrease in O.D. of the overnight growing culture. The trend seems to be reducing up to the middle AgNP concentration, 200µL for AgNPs synthesized using Arjun, Turmeric and curry leaves plant extracts and 300µL for AgNPs synthesized using Ashwagandha plant extract. The O.D. is seen to slightly increase as concentration increases beyond 300µL; this could be due to the colour of the synthesized AgNP solution in the media.

For *S. aureus*, it was observed that with an increase in the concentration of Turmeric and Arjun AgNP, the O.D. decreased with 300µL showing the maximum inhibition for AgNPs synthesized using arjun extract and with 400 µL for AgNPs synthesized using Turmeric extract (Figure 2b). The increase in O.D. at 500 µL can be due to the contribution of the colour of the AgNP solution itself. There was no such trend observed for curry leaves and ashwagandha nanoparticles. The highest inhibition was observed at 200 µL volume of AgNPs synthesized using curry leaves and ashwagandha extracts.

AgNPs synthesized using plant extracts were observed not to significantly affect the growth of *S. cerevisiae* at any volume from 10 µL to 500 µL after 48 hours of incubation (Figure 2c). This gives us the idea that the same lower volumes of AgNPs are highly effective as an antibacterial agent against prokaryotes but are not harmful in a eukaryotic organism, making it a potential antibacterial agent and can replace many antibiotics that have developed resistance in the microorganisms. However, a slight reduction in the growth is observed compared to the positive control which gives us an idea that unregulated use of the synthesized AgNPs can be toxic.

Therefore, a comprehensive study of the mechanism of action and downstream processes should be carried out before using the AgNPs in medicinal or environmental applications. The AgNPs showed antibacterial activity against both *E. coli* and *S. aureus* but showed no significant effect on the growth of *S. cerevisiae*. Therefore, this property of the AgNPs was used to treat water contaminated with 10^3 CFU/mL *E. coli*.

Treatment of Contaminated Water: The primary contaminant found in drinking water and wastewater was *E.coli*. Water spiked with *E.coli* was used to check for the ability of AgNPs to treat contaminated water efficiently. A reduction in the number of CFU/ml was observed in water with a load of 10^3CFU/mL *E.coli* when treated with AgNPs. With just 10 µL of the synthesized silver nanoparticles, a complete reduction in the number of colonies formed was observed for chemically synthesized silver nanoparticles and AgNPs synthesized using turmeric and tulsi extracts in just 10 minutes and 20 minutes using AgNPs synthesized using curry leaves (Figure 3). End-point assay was carried out to determine the efficiency of water treatment using ashwagandha and arjun nanoparticles. Increasing volumes of AgNPs were added and the O.D. was measured at 0 minutes i.e. immediately after treatment with AgNPs.

It was observed that AgNPs synthesized using arjun extract showed complete inhibition at 0 minutes with as low as 5 µL of the AgNPs. AgNPs synthesized chemically and using ashwagandha extract, showed complete inhibition with 30 µL of AgNPs (Figure 4). Therefore, the antimicrobial property of AgNPs synthesized using arjun, turmeric and tulsi plant extracts should be explored further for the treatment of water, as it is a non-toxic, less time consuming and less expensive process as compared to other physical methods and can also be used to develop potable water drinking devices.

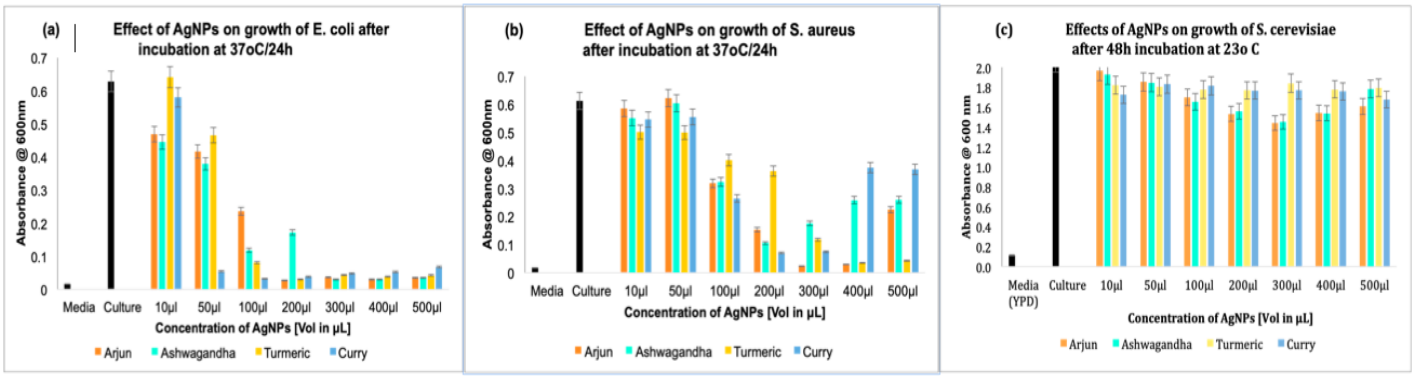

Figure 2: Effect of increasing concentrations of AgNPs on the growth of a) *E. coli*, b) *S. aureus* and c) *S. cerevisiae*

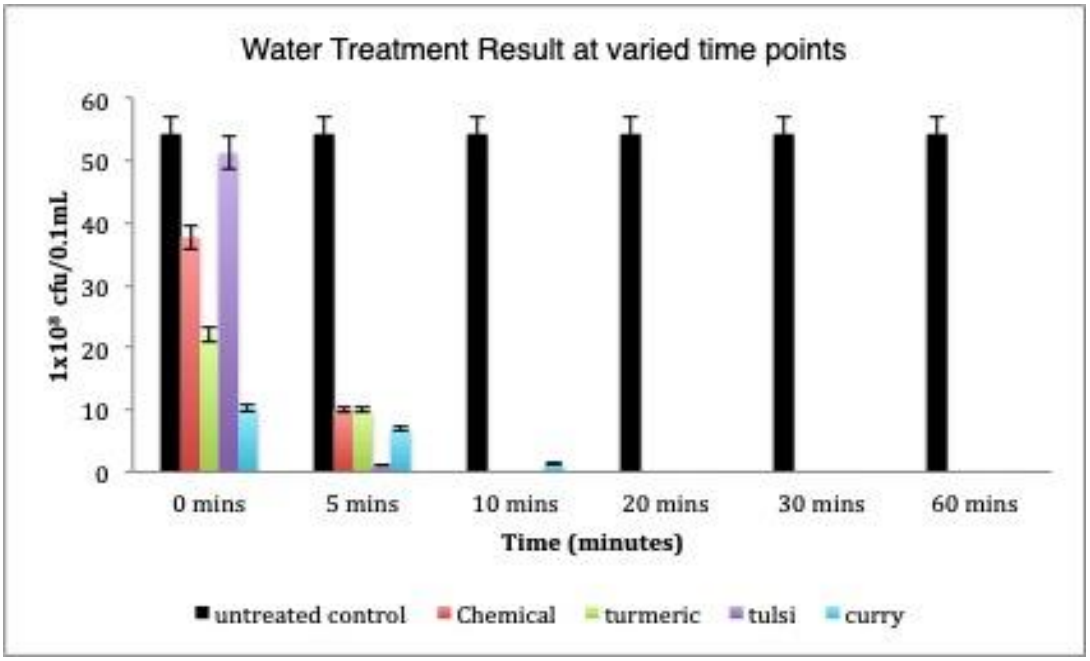

Figure 3: Water treatment with synthesized AgNPs using Turmeric, Tulsi and curry leaves extracts at various time intervals

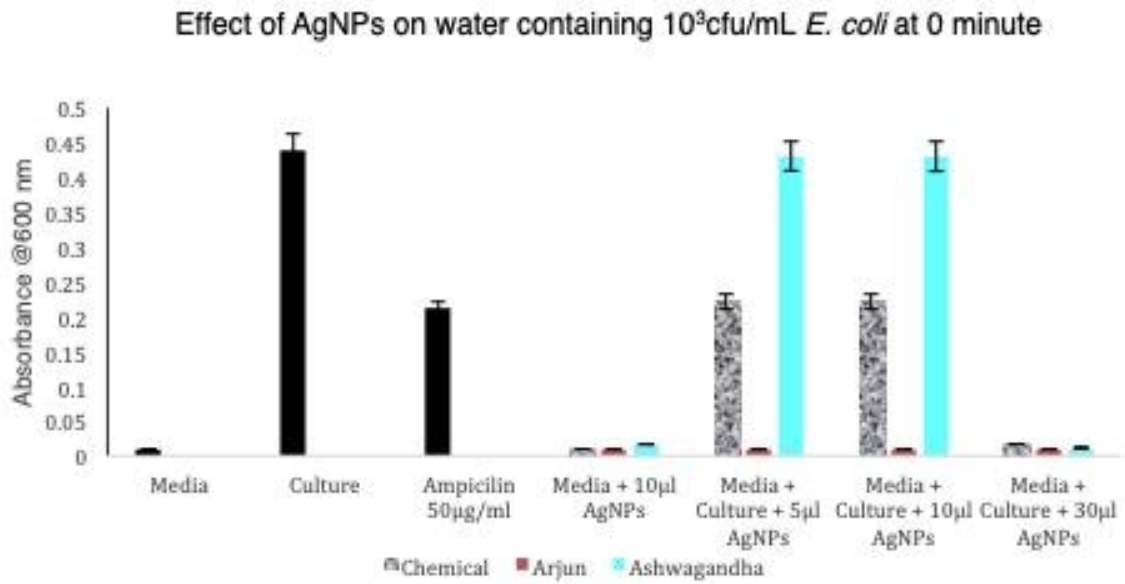

Figure 4: Water treatment with synthesized AgNPs using Arjun and Ashwagandha extracts at increasing volumes of AgNPs

Effect of AgNPs on Advanced Glycation End products: The effect of AgNPs synthesized using Arjun, Ashwagandha, Aloe vera, Turmeric and curry leaves extracts on AGEs was studied by measuring the UV absorbance at 420nm. For 3mg/mL of BSA and 6mM methylglyoxal, browning was observed in 7 days of incubation at 37°C. BSA without MG or AGNPs showed the lowest absorbance value whereas BSA and MG mixture showed comparatively high absorbance indicating the formation of advanced glycation end-products. BSA and MG mixture treated with AgNPs synthesized using Ashwagandha, curry leaves and *Aloe vera* showed a reduction in absorbance values indicating inhibition of formation of AGEs with increasing volumes of AgNPs (Figure 5). As high as 88.80% decrease in absorbance was observed with 200 µL of curry leaves AgNPs while only 10.32% reduction at 50 µL AgNPs was observed.

Similar inhibition was observed at 200 µL of Ashwagandha AgNPs (76.51%) and *Aloe vera* AgNPs (81.50%). The results obtained using Ashwagandha, curry leaves and *Aloe vera* AgNPs are consistent with previous studies on the inhibitory effect of AgNPs synthesized using *Aloe vera* on AGEs formation[3,12].

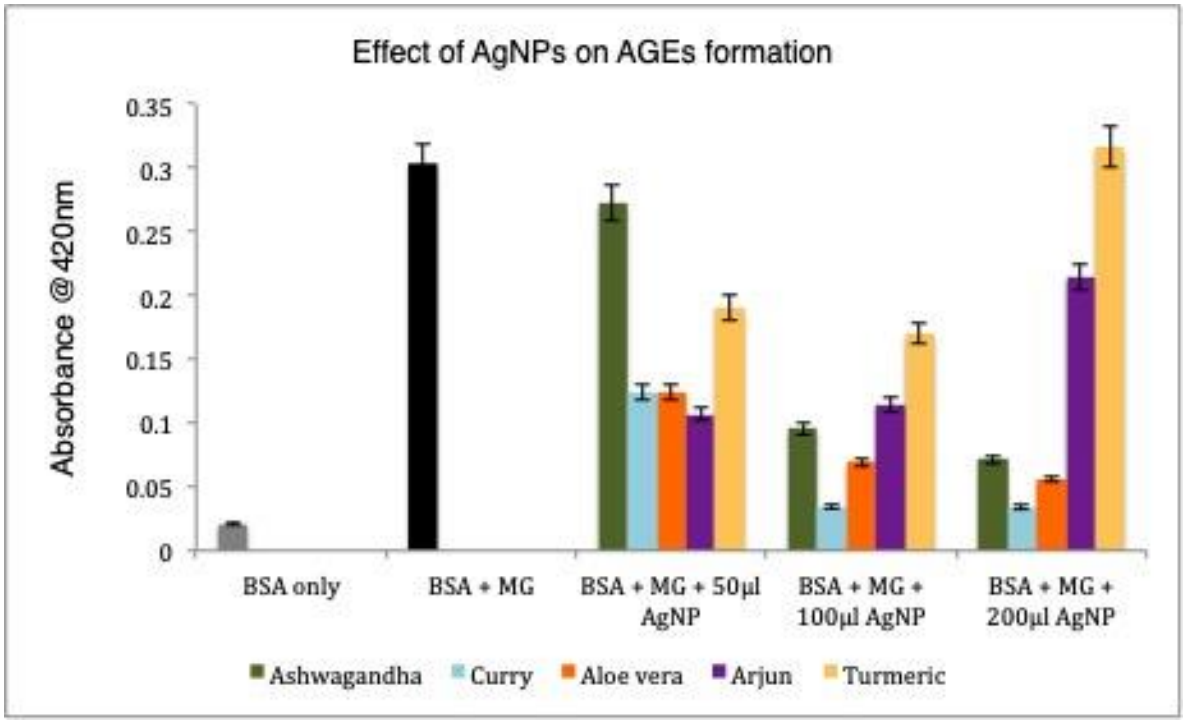

Figure 5: Effect of AgNPs on AGEs with increasing concentrations of AgNPs. UV absorbance values of BSA and MG incubated at 37ºC/7 days observed at 420nm with increasing volumes of AgNPs

BSA and MG mixture were treated with AgNPs synthesized using Arjun and Turmeric plant extracts, the absorbance increased with increasing volumes of AgNPs. For AgNPs synthesized using Arjun, the highest inhibition was obtained at 50 µL (64.87%) and lowest at 200 µL (29.36%). No inhibition was observed at 200 µL for turmeric AgNPs. However, UV absorbance is just a confirmatory test for the browning reaction indicating AGE formation and further specific tests like fructosamine assays and NBT assays that detect the presence of protein-bound Carbonyl compounds.

The inhibitory effect of increasing concentration of AgNPs synthesized using various plant extracts on formation of AGEs was analyzed by 2-way ANOVA (Microsoft Excel, 2011). The results obtained with the statistical analysis are significant. AgNPs exhibit varied effects on AGEs formation based on increasing volumes and different sources of plant extract used for synthesis of AgNPs. Although AgNPs demonstrate to be a promising candidate as a potential antiglycating agent, each AgNP synthesized using different plant extracts should be treated separately and their dosage concentration and mechanism of action should be studied individually.

The current study shows that green synthesized silver nanoparticles using Ashwagandha, *Aloe vera* and curry leaves extracts show anti-glycating properties in a concentration-dependent manner that can work as therapeutic agents in the treatment of secondary complications of diabetes. An in-depth and extensive study of the properties and mechanism of AgNPs synthesized biogenically must be carried out to better understand their role in medicinal and therapeutic applications.

Conclusion

The potential of silver nanoparticles as an antibacterial agent with bactericidal effects on multidrug-resistant pathogens has been long established[20]. The result of our study validates that silver nanoparticles were synthesized using various plant extracts like Turmeric, *Aloe vera*, Arjun, Ashwagandha, Curry leaves and Tulsi which were eco-friendly, free of toxic chemicals, easy to synthesize, low cost and remained stable for over one year. They show antibacterial activity against both *E. coli* and *S. aureus*. The synthesized AgNPs show no significant effect on the growth of *S. cerevisiae*.

Hence, they can be assumed to be less toxic in eukaryotes as compared to prokaryotes and therefore can be used for environmental and therapeutic applications in a regulated manner. Since *E.coli* is the major contaminant found in drinking water[21], the AgNPs were used to treat water contaminated with *E. coli* and complete inhibition was observed when water spiked with *E.coli* was treated with 30 µL of synthesized AgNPs within 10 minutes. Silver nanoparticles synthesized using these plant extracts can prove to be a cheap, quick, yet effective way to treat contaminated drinking water.

AgNPs synthesized using *Aloe vera*, Ashwagandha and curry leaves plant extract also have anti-glycating potential and were aligned with earlier findings[3]. Nanoparticles are also known to induce cytotoxic pathways[14,15]. Therefore, a comprehensive study of the antiglycating ability of the AgNPs[12,26] and their bio distribution and downstream pathways should be performed to understand their role in therapeutic applications better.

The green synthesized nanoparticles using Turmeric, *Aloe vera*, curry leaves, Arjun, Ashwagandha and Tulsi plant extracts show enormous acts of exploration potential and hence detailed studies should further be carried out to understand their morphology, mechanisms and applications better. Silver nanoparticles synthesized using a green approach hold seemingly endless potential.

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