



A REVIEW ON SOME OF THE GREEN SYNTHESIS OF SILVER NANOPARTICLES WITH MOLECULAR DOCKING ACTIVITIES

*Mounika Perli¹, Nayomi Gadikoyya², Meruva Venkata Naresh³, Shaik Magbul Basha³,
Dr. J.N. Suresh Kumar⁴

Assistant Professor¹, IV B. Pharmacy^{2,3}, Principal⁴

Narasaraopeta Institute of Pharmaceutical Sciences

Kotappakonda Road, Yallamanda, Narasaraopet, Palnadu, Andhra Pradesh, India-522601

ABSTRACT: Nanotechnology refers to the synthesis of nanomaterials (1-100nm) and their applications. Nanoscience can deal with individual atoms and molecules. In recent times, an agreement has started to rise about the informatics foundation expected to accumulate, curate, and share data among every one of the fields in nanotechnology. Nano informatics is fulfilling this demand. It is the science about figuring out which data is important to the nanoscale science and after that creating and implementing viable systems for gathering, approving, sharing, analyzing, modeling, and applying that information. Nano informatics is essential for efficient production and relative description of nanomaterials. The present study focused on the prediction of interactions of three ligands i.e. silver nanoparticles, tyrosine capped silver nanoparticles, and silver oxide nanoparticles with proteins. In this we have reviewed the green synthesis of silver nanoparticles (SNPs) using plant extracts is an eco-friendly methods. This study analysed the molecular docking of the Silver Oxide Nanoparticles (Ag₂O-NPs) synthesized from the novel medicinal plants.

KEYWORDS: Silver Nanoparticles, Different Activity, Molecular Docking, SNPs, AgNP

INTRODUCTION

Silver nanoparticles have been utilized for many applications counting as anti-viral and anti-bacterial agents. They are being used in healthcare products, beauty care products, the food industry, pharmaceutical industries, and medical and electronic devices. The biological characteristics of silver nanoparticles depend on various parameters. In systematic and local administration, bioavailability of therapeutic agents get improved because of the physiochemical properties of the nanoparticles. Silver nanoparticles produce by using the berry extract of Sea Buckthor, display a broad range of antioxidant, anti-inflammatory and anticancer activities. AgNPs are proven to be safe antibacterial and antibiofilm compounds against MDR K. pneumonia. Silver nanoparticles produced by Sphingobium sp. MAH-11 may act as an intense antimicrobial agent in many treatments. Hence, the synthesis of silver nanoparticles in a controlled manner is useful in several biomedical applications.

Currently, medication and immunization advancement for the evacuation of different viral ailments are under critical consideration, various viral strains have been developed that are no more sensitive to drugs and vaccines. So it is imperative to present the multidisciplinary approaches with the established epidemiology, alongside the clinical phases to present a new drug or vaccine which possesses great effectiveness against the resistant strain. Nanotechnology has revolutionized the field of Medici Chemicals and Reagents Organic solvents used in this study, including n-butanol, ethyl acetate, acetone, dichloromethane, and petroleum ether (b.p. 60–80 °C) were of analytical grade and distilled prior to use. Dimethylsulfoxide (DMSO) was used in the preparation of silver nanoparticles. All these solvents were purchased from El-Nasr Company for Pharmaceuticals and Chemicals, Egypt. Solvents of HPLC grade such as acetone, methanol and methanol were obtained from SDFCL sd fine-Chem Limited, India. Both silver nitrate (AgNO_3 ; purity $\geq 99.5\%$) and the ion exchange resin were purchased from Sigma-Aldrich, Germany. Celecoxib and indomethacin were purchased from Sigma-Aldrich, Germany and used as standard anti-inflammatory drugs.

SYNTHESIS OF SILVER NANOPARTICLES (SNPS)

SILVER NANOPARTICLE SYNTHESIS FROM CARICA PAPAYA

Fresh C. Papaya leaves were obtained from the Namakkal region of Tamil Nadu, India. The leaves were cleaned and washed with water to remove dust particles before use. About 10 g of finely cut leaves were placed in a 250 ml Erlenmeyer flask containing 100 ml of sterile double-distilled water. The mixture was boiled for 20 min, cooled, and filtered. The filtered extract was stored at $-15\text{ }^\circ\text{C}$ for the synthesis of silver NPs.

BIOSYNTHESIS OF SILVER NANOPARTICLES

Silver nitrate (AgNO_3) was used as the precursor for the synthesis of Ag NPs. About 10 ml of the leaf extract was added to 90 ml of 1 mM aqueous solution of AgNO_3 in a 250 ml. brownish yellow color conical flask and maintained at $27\text{ }^\circ\text{C}$. The reaction was performed for 24 h and the appearance of a indicated Ag NP formation

GREEN SYNTHESIS OF SILVER NANOPARTICLES OF LAMPRANTHUS COCCINEUS AND MALEPHORA LUTEA AQUEOUSEXTRACTS

The collected soft coral was freeze-dried, then extracted with methylene chloride – methanol (1:1) until exhaustion.⁵⁰ The concentrated organic extract (24.0 g) was suspended in distilled water and extracted successively with different organic solvents, including petroleum ether, ethyl acetate and n-butanol. The remaining mother liquor was deprived of its content of sugars and salts by an ion exchange resin using acetone. The organic phase in each step was separately concentrated under vacuum, yielding the petroleum ether fraction I (10.0 g), the ethyl acetate fraction II (3.0 g), the n-butanol fraction III (3.0 g), and the acetone fraction IV (200.0 mg). The total extract and its derived fractions were kept at $4\text{ }^\circ\text{C}$ for metabolomics and biological investigation.⁵¹

The green silver nanoparticles were prepared by separately dissolving 0.005 g of each of the petroleum ether and ethyl acetate fractions in 1 mL DMSO. Then, 0.2 mL of each sample solution were added to 10 mL of 1 mM AgNO_3 and the reaction mixture was kept for 48 h at room temperature.⁵² Unfortunately, both the n-butanol and acetone fractions failed to be converted into nanoparticles, as clearly confirmed by monitoring the color change of the reaction mixtures during their preparation.



Fig.1

SYNTHESIS OF SILVER NANOPARTICLES:

The extract of neem leaves (18 ml) was mixed with 50 ml of 1mM Silver nitrate (AgNO_3) solution in 1:2.78 ratio in a conical flask under aseptic condition. The flask was kept in shaking water bath at 37°C in dark for 5 hours. A change in the color was observed indicating the formation of Silver nanoparticles. The quality of the Silver nanoparticle prepared was checked before testing its antimicrobial effect. The antimicrobial effect of the Silver nanoparticle, synthesized using neem, was studied.

SYNTHESIS OF CLOVE AGNP'S

The synthesis procedure was carried out based on the protocol . About 1 ml of clove aqueous extract was added to 10 ml of 1 msilver nitrate solution with constant stirring for about 2 hrs at room temperature. The reaction mixture was checked periodically for color change. After 2 hrs of incubation time, the yellowish-green color was observed, which was then centrifuged at 3000 rpm for 10 minutes. The pellet contained the nanoparticles, which was separated and stored in a sterile Eppendorf's at 4°C .

SYNTHESIS OF THREE DIFFERENT SILVER NANOPARTICLE PREPARATIONS

Carbon coated silver nanoparticles tested in this study were obtained from Nanotechnologies, Inc. and used without further treatment. For more information about the synthesis of these nanoparticles, please visit <http://www.nanoscale.com> PVP-coated silver nanoparticles were synthesized by the polyol method using glycerine as both reducing agent and solvent. Silver sulfate (Ag_2SO_4 , reagent grade) and poly (N-vinyl-2-pyrrolidone) (PVP-K30, MW = 40,000) were purchased from Sigma Aldrich and 1,2,3-Propanetriol (Glycerin, >99%) was purchased from Fischer Chemicals, all the materials were used without any further treatment. Briefly, we added 0.2 g of PVP to a round bottom flask following by the addition of 30 mL of glycerin. Once PVP was dissolved, we increased the temperature to 140°C . After 30 minutes we added 2 mL of 0.015 M Ag_2SO_4 and left to react for 1 h. Silver nanoparticles directly conjugated to bovine serum albumin (BSA) protein molecules were produced as following described. Silver nitrate (AgNO_3 , 0.945 M), sodium borohydride (NaBH_4 , 99%) and 200 proof spectrophotometric-grade ethanol were purchased from Aldrich. Bovine serum albumin (BSA) was purchased from Fisher and was used without further treatment. Briefly, sodium borohydride was added to an aqueous solution of silver nitrate and BSA under vigorous stirring. The molar ratio of $\text{Ag}^+:\text{BSA}$ was 28:1, and the molar ratio of $\text{Ag}^+:\text{BH}_4^-$ was 1:1. The reaction volume was 40 mL, and contained $13.50 \mu\text{mol}$ BSA. The reaction was allowed to proceed for 1 h, and the product was purified by precipitation at -5°C , followed by cold ethanol filtration.

HIV-1 STRAINS AND CELL LINES

HIV-1IIB laboratory strain of HIV-1 an X4 wild type (wt) virus was obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH. CD4+ MT-2 cell line was obtained from the American Type Culture Collection. The cMAGI HIV-1 reporter cells were a generous gift from Dr. Phalguni Gupta from the University of Pittsburgh. All other reagents used were of the highest quality available. cMAGI

cells were cultured in DMEM Dulbecco's Modified Eagle Medium (DMEM) (1X) liquid without sodium phosphate and sodium pyruvate. The medium contained 4,500 mg/L D-glucose and L-glutamine (Invitrogen, Paisley, UK), with 10% fetal calf serum (FCS), 0.2 mg/mL geneticin (G418), and 0.1 µg/mL puromycin. MT-2 cells were cultured in RPMI 1640, containing 10% fetal calf serum (FCS) and antibiotics HIV-1III B primary clinical isolates were propagated by subculture in MT-2 and cMAGI cells. HIV-1III B was reproduced according to the DAIDS Virology Manual for HIV Laboratories, version 1997, compiled by Division of AIDS of the National Institute of Allergies and Infectious Diseases and the National Institute of Health, and Collaborators. Aliquots of cell-free culture viral supernatants were used as viral inocula. All the work related to HIV-1 cells, except for TEM analysis, was done in a Biosafety Level 3 (BSL-3) Laboratory.

MOLECULAR DOCKING ACTIVITIES OF SILVER NANO PARTICLES

Nanoinformatics is an emerging science. It contains databases and tools. Some of them are Nanomaterial Biological Interactions Knowledgebase, InterNano, Nanoparticle Information Library, etc. Nowadays, as nanomedicines are being used and found to have high efficiency, molecular docking of Page 5/28 nanomaterials is in trend. In drug discovery, docking is a critical computational technique predicting protein-ligand interactions. The two fundamental characteristics of docking programs are docking precision and scoring reliability. Docking accuracy demonstrates how similar the predicted ligand to the experimental data, whereas scoring reliability positions ligands because of their affinities. Docking accuracy evaluates searching algorithm and scoring reliability assesses scoring functions. In the docking program, the numerous searching algorithms work differently as for randomness, speed, and the area covered. Many searching algorithms show good performance when used against the known structure. Presently, numerous sorts of docking programs are easily accessible, among which, AutoDock is frequently used and openly accessible. As protein-nanoparticle interactions are not easy to examine utilizing experimental techniques, molecular docking tools facilitate to ease this difficulty.

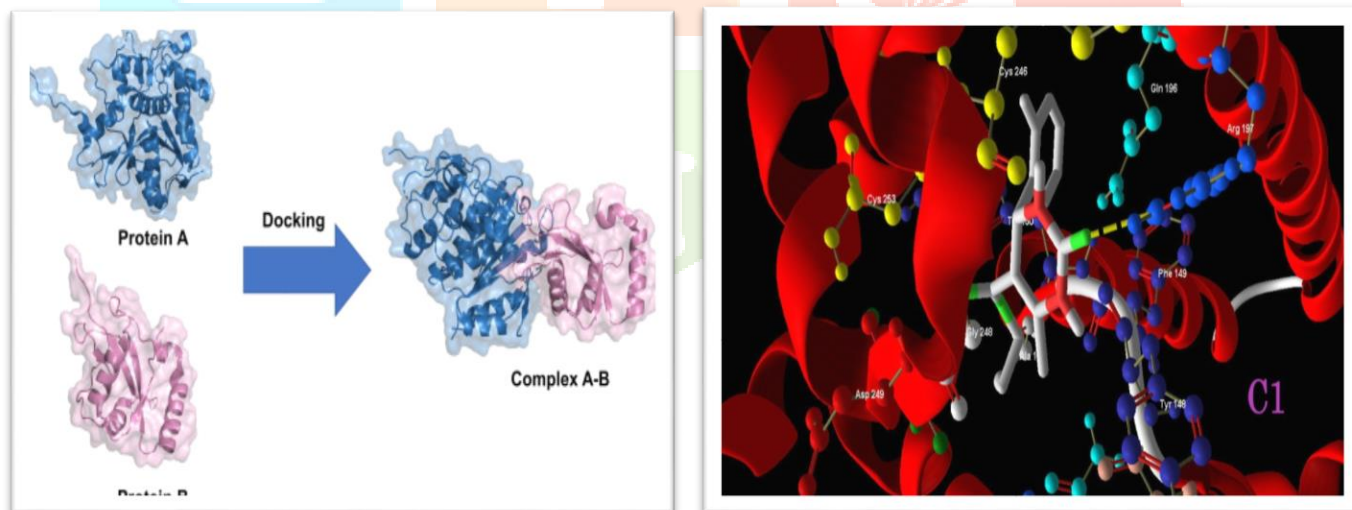


Fig-2

ANTIVIRAL ACTIVITY

To determine the antiviral activity of the phytochemical constituents of *C. papaya*, the three-dimensional (3D) crystal structures of dengue type 2 virus non-structural protein were retrieved from the Protein Data Bank database and the 3D structures of the phytochemicals was obtained using ACD/ChemSketch and converted into PDBQT files using PyRx. To explore the binding affinities between the receptors and the ligands, an automated flexible docking of ligands was performed using AutoDock Vina. The grid maps representing the protein binding sites for docking were calculated using AutoGrid. A grid of $81 \times 55 \times 91$ points in each dimension of NS1, with a spacing of 0.375 Å between the grid points, was obtained using AutoGrid. Gasteiger charges on the atoms of both ligands were calculated using AutoDock tools. All possible torsions of the ligand molecules for the docking algorithm were considered using the AutoTors tool of AutoDock, and docking was performed using the following parameters: no. of docking trials: 10, population size: 150, maximum number of energy evaluations: 250000, maximum number of generations: 27,000, mutation rate: 0.02,

cross-over rate: 0.8, elitism value: 1, and other parameters: default values. Finally, the docking pose with the best binding affinity score (kcal/mol) for each ligand against each receptor was obtained, and this orientation were selected for the binding interaction studies. The docking interactions studies were performed using receptor–ligand interaction options in Discovery Studio v2.5

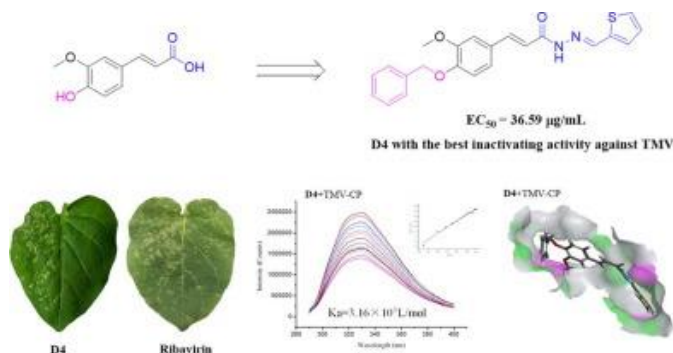


Fig-3

ANTICHOLINESTERASE ACTIVITY

This study was conducted on adult male Albino rats of Sprague-Dawley of 130–150 g body weight in compliance with the guidelines for animal experiments set by the ethical committee of the National Research Centre and animals were treated in accordance with Canadian Council on Animal Care (CCAC). The unnecessary disturbance of animals was avoided. The animals were treated gently; squeezing, pressure and tough maneuver were avoided. The study was also approved by the Research Ethics Committee for Animal Experimentation, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Helwan University, Egypt. They were kept under the same hygienic conditions and on a standard laboratory diet consisting of vitamin mixture (1%), mineral mixture (4%), corn oil (10%), sucrose (20%), cellulose (0.2%), pure casein (95%) and starch (54.3). A probability value of less than 0.05 was considered statistically significant ($P < 0.05$), after synthesis and characterization of SNPS.

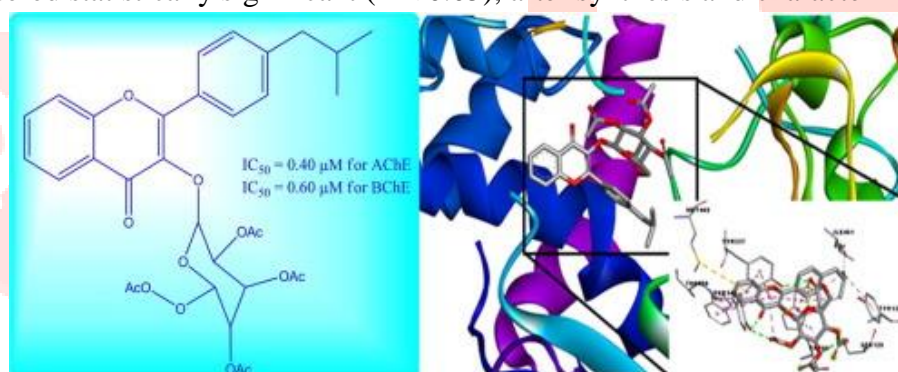


Fig-4

ANTI-ALZHEIMER ACTIVITY

Three crystal structures were selected to study the anti-Alzheimer activity of the ligands. The first crystal structure (PDB ID: 4BDS) is for Human butyryl cholinesterase. The 4BDS crystal has a co-crystallized ligand, tacrine, that was utilized in defining the active site. The second crystal structure (PDB ID: 4M0E) is for human acetylcholinesterase with co-crystallized ligand (dihydratanshinone I) that was used to define the active site. The third crystal structure (PDB ID: 4ZBD) is for glutathione transferase. The 4ZBD crystal's binding site was defined by co-crystallized glutathione. Hence, three docking sites were used to study the binding patterns and affinities of the ligands. In all dockings, a grid box of dimensions 40 grid points and spacing 0.375 was centered on the given co-crystallized ligand. Four conformations were generated for each ligand using OpenBabel, and docking was performed via Autodock4 implementing 100 steps of the genetic algorithm while keeping all the default setting provided by Autodock Tools. Visualization was done using the Discovery studio program.

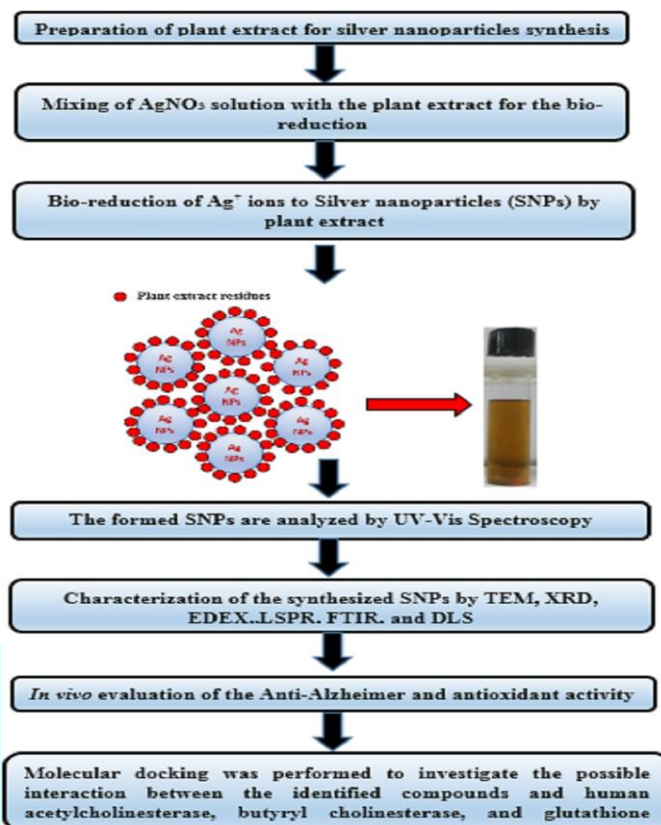


Fig-5

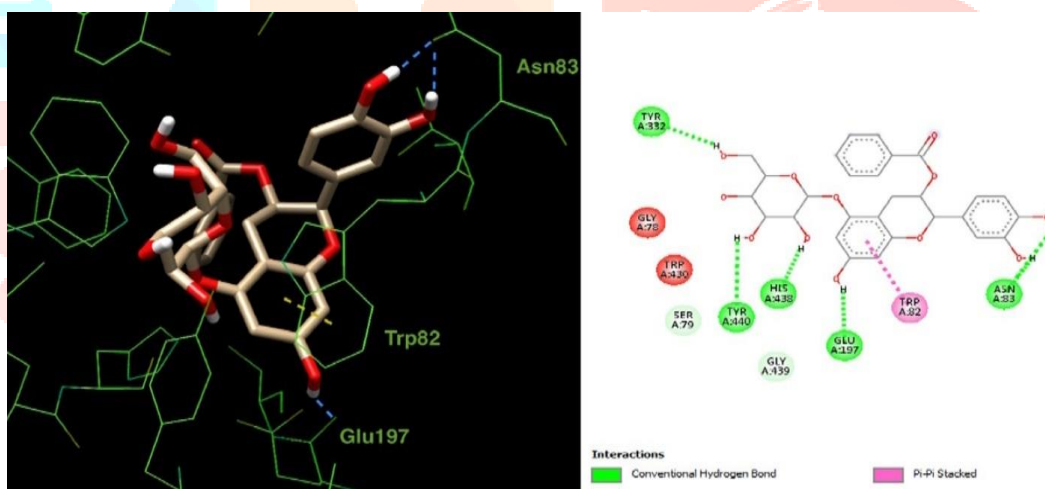


Fig-6

ANTI-INFLAMMATORY ACTIVITY

Silver nitrate and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) were obtained from Sigma-Aldrich. Butylated hydroxyanisole (BHA) was purchased from Hi-Media Laboratories Pvt. Ltd. Solvents were purchased from Loba chemicals.

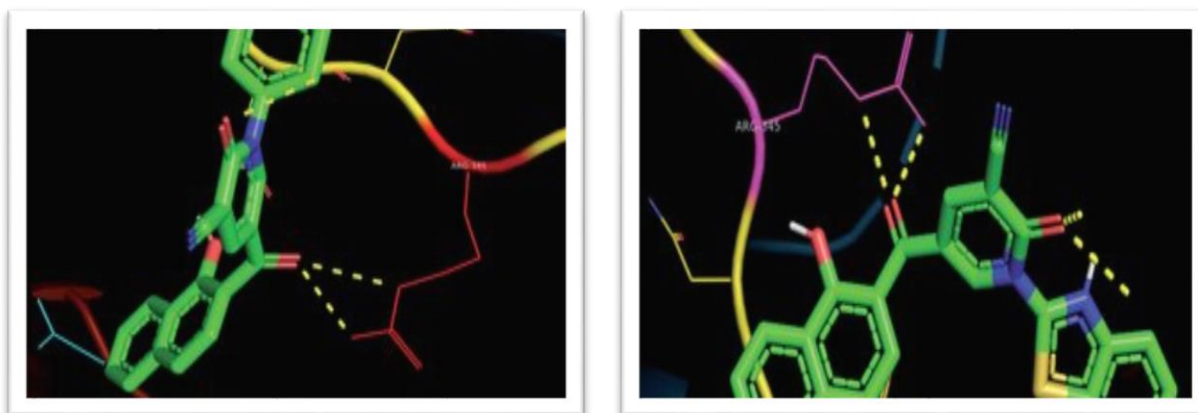


Fig-7

In silico molecular docking, the study was performed using Schrödinger Maestro to identify the anti-inflammatory property of aqueous extract of clove. Phytochemicals of clove were identified through GC-MS method. The two-dimensional (2D) compounds were retrieved from PubChem database [] and then subjected to the LigPrep module of Schrödinger Maestro, where the compounds were converted from 2D to 3D, addition of hydrogens, generation of ionization states and assigning proper bond lengths, bond angles, torsion angles, correct chirality, stereochemistry, and ring conformation. The 2D X-ray coordinates of protein target beta-interleukin was downloaded from RCSB-protein data bank using the respective id: 2NVH.

ANTIPROLIFERATIVE ACTIVITY

More than 100 HSA structures are available in the RCSB Protein Data Bank. Selected a structure (PDB ID: 5ID7)52 on the basis of resolution, the number of missing residues, and the R factor out of 105 human serum albumin structures, and its coordinates were retrieved from RCSB Protein Data Bank. The nanoparticle used in this study is the silver nanoparticle (AgNP). The spherical structure of the AgNP has a diameter of 4.5 nm, taken from an earlier study.⁵⁴ The AgNP structure is made up of 3871 Ag atoms. The Lennard-Jones parameters for the AgNP were considered from the Heinz group.⁵⁵ The AgNP and protein conjugates were prepared with the molecular modeling system Chimera.⁵⁶ We have considered five different orientations of the protein to interact with the NP. As mentioned above, the HSA protein has multiple active sites spread in three domains, and each of them has been reported to carry different drug molecules. The AgNP was placed near the active sites of individual domains to observe the effect of NPs on protein conformation. Only one NP was considered in the first four orientations, and two nanoparticles of the same size were used in the last conjugate. The orientations are considered such that the AgNP encompasses all the domains of the protein. In all of the protein–NP conjugates, the exterior atoms of the NP were kept in a range of 2–4 Å from the protein's surface. The coordinates of the five orientations of the HSA protein–AgNP conjugates were further used to carry out dynamic simulations

ANTIOXIDANT ACTIVITY

In order to explore the basis of the EDC-crosslinking initiation, docking studies were performed between a synthetic collagen peptide and different lengths of chitosan polymers, including 3mers, 6mers, 9mers, and 12mers. Chitosan oligomers were set as the models for Csnp here, owing to the violently growing probabilities of the flexible structure simulation as chitosan polymers extended. The model of the synthetic collagen peptide was obtained from the crystal structure of Staphylococcus aureus (S. aureus) collagen binding collagen adhesin (CNA) in complex with the collagen peptide (PDB: 2F6A) . The chitosan polymers were generated by ChemDraw Professional 16.0 and converted to 3D models by iBabel 5.0 . After the coordinate preparation, the collagen peptide was set as the macromolecule, while the chitosan polymers were the ligands. Using AutoDock Vina.

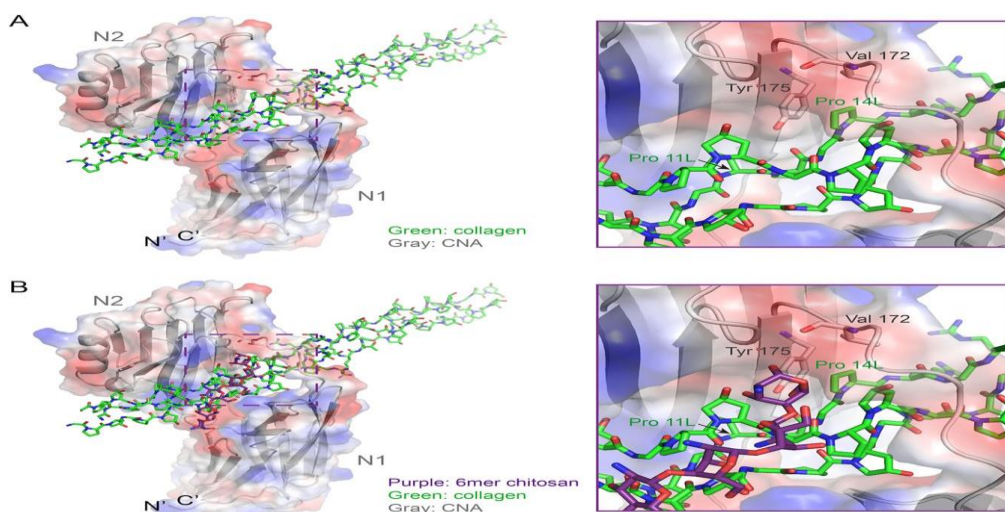


Fig-8

Conclusion

To the best of our knowledge, the present work reports for the first time the green syntheses of size adjusted AgNPs. The docking results of different proteases shows that AgNPs shows broad range of activities.

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