



Original article

Green synthesis, characterization and biological activity of *Solanum trilobatum*-mediated silver nanoparticles

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ABSTRACT

Biologically inspired synthesis of nanoparticles was found to be more attractive in metal nanoparticle synthesis. The present study reported an *in-situ* biogenic synthesis of silver nanoparticles (AgNPs) using *Solanum trilobatum* aqueous leaf extract. On this basis, the aqueous leaf extract of *S. trilobatum* acted as a reducing agent and stabilizing agent to synthesize highly stable AgNPs at ambient temperature. Eventually, the synthesized and stabilized AgNPs surface plasmon resonance was near 430 nm through a UV–visible (UV–vis) spectrophotometer. Here, the stability of the silver colloids monitored through zeta potential and mean particle size was evaluated through diffraction light scattering (DLF). Further, the average particle size was found to be 27.6 nm and spherical, confirmed with transmission electron microscopy (TEM). Also, colloidal AgNPs and aqueous extract are found to be rich sources of antioxidants and exhibit higher free radical scavenging ability. Thus, efficient inhibition with COX1 and COX2 enzymes and the protective effect with human red blood cell (HRBC) membrane stability showed significant results. These features are promising, suggesting the possibility of the AgNPs to be useful to disease-modifying for treating inflammatory disorders and associated complications.

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1. Introduction

Regulation of oxidative stress manifests potential therapeutic targets in various cancers and neurological disorders (Barnham et al., 2004). Oxidative stress is correlated with reactive oxygen species (ROS) fluctuations in macromolecules, like lipids, proteins, carbohydrates, and nucleic acids (Rahal et al., 2014). The peroxisomal oxidation in mitochondrial fatty acids can generate ROS, which consumes excessive oxygen. Among the consequences, the accumulation of free radicals and oxidative phosphorylation found in

the mitochondrial respiratory chain down-regulates oxygen metabolism (Ježek and Hlavatá, 2005). Nowadays, the field of neurobiology includes neurogenesis neurotrophins, corticosteroids, inflammatory cytokines, mitochondrial energy generation, and oxidative stress to explain the concepts of bipolar disorder (Berk et al., 2011). Additionally, ROS provokes the mitochondrial permeability abnormalities and induces signal catalyzing to prognoses autophagy, apoptosis, and necrosis (Montaigne et al., 2012). In addition, dysregulation of apoptosis results in inflammations and associated neurodegenerative disorders, arthritis, and types of cancer (Hwang and Kim, 2015). The traditional herbs are polyphenols rich and influential in regulating inflammation and associated symptoms (Singh et al., 2011). Conventionally, these phytochemicals had profound regulation with transcription factors, nuclear factor kappa-light-chain-enhancer of activated B cells, Tumour Necrosis Factor-alpha, Interleukin -1 β , c-Jun N-terminal kinase, Interleukin -6, Mitogen-activated protein kinase 1, Interleukin 1 beta, Mitogen-activated protein kinases and COX-2, which

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involved in the inflammation pathway (Rosillo et al., 2019). Further, these phytochemicals scavenge free radicals and act as anti-liperoxidants, thus, preventing collagen from superoxide anion radical distress (Juliano and Magrini., 2018). In addition, these phytochemicals attain potential positive lipoxygenase inhibition and antioxidant properties; they have been useful to treat inflammatory diseases (Loke et al., 2008). Besides, the phenolic compound acts as chelating/reducing and capping molecules in biogenic nanoparticle synthesis (Sengani et al., 2017).

The transcriptomes analyzed from *Solanum trilobatum* found that the gene expression of flavonoid enzymes Flavonol synthase, Chalcone Isomerase, and Naringenin-3-dioxygenase was significantly high compared with those of others other secondary metabolites (Lateef et al., 2018). Furthermore, comparing these metabolites, the Chalcone Isomerase transcriptome gene expression resulted more present in major metabolic pathways. In general, the Chalcone Isomerase enzyme plays a potential role in suppressing oxidative stress and ultimately possesses protective against cardiovascular disorder (Karim et al., 2021). Also, studies reveal that anti-inflammatory and anti-analgetic compounds like β -solamarine, solasodine, solanine, glycoalkaloid, and diosgenin compounds are isolated from this plant (Nivedithadevi et al., 2012). The plant crude extracts (Mathivanan et al., 2010; Govindarajan, 2011), biological molecules (Govindarajan et al., 2013) and synthesized silver nanoparticles (Roni et al., 2015; Govindarajan and Benelli, 2017; Balalakshmi et al., 2017; Suganya et al., 2017) have to possess various biological activities. The present study reported the biogenic synthesis of silver nanoparticles (AgNPs) using *S. trilobatum* leaf extract and their biological activities.

2. Materials and methods

2.1. Preparation of *S. trilobatum* leaf extract

S. trilobatum L. leaves extract prepared using shade dried and powdered. Then, 5 g of dried leaf powder was homogenized with 100 mL of double distilled water and heated for 30 min at 90–95 °C in a temperature-controlled water bath. Further, the resultant solution filtered through a 0.22 mm pore-sized cellulose nitrate membrane to remove debris. This extract was stored in a refrigerator and used to prepare nanoparticles.

2.2. Silver nanoparticle (AgNPs) synthesis

About 10 mL of freshly prepared *S. trilobatum* leaf extract was added to 5 mL of AgNO₃ (0.01 M) and mixed thoroughly at ambient temperature. AgNPs' formation was observed through a visual color change from yellow to reddish-brown and further reduction kinetics was monitored spectrophotometrically.

2.3. Characterization of AgNPs

The colloidal AgNPs solution was diluted into five folds with deionized water to proceed with characterization using double beam UV–vis spectroscopy (Jasco V-670 UV–visible double beam spectrophotometer). In this analysis, the spectra were measured between 200 and 800 nm using deionized water as blank. The external stability and the average particle size distribution were analyzed at an angle of 90° through a zeta sizer (Horiba Scientific SZ-100, UK). The reduced colloidal solution was centrifuged at 10000 rpm for 30 min to get precipitated AgNPs. The crystalline structure of AgNPs, the dried nanoparticles coated on the XRD grid and the spectral scanning range of 10° to 90° (2 θ value) were

recorded. The purified AgNPs were subjected to high-resolution Transmission electron microscopy (TEM) (PHILIPS CM200) analysis for size and shape. In this experiment, well-dispersed nanoparticles coated on the Cu grid to get high-resolution TEM images and selected area electron diffraction (SAED) pattern at 2.4 Å resolution accelerated with 20–200 kV. Further, the *S. trilobatum* dried leaf extract was pelleted with KBr and subjected to Fourier-transform infrared (FTIR) spectroscopy (JASCO FT-IR 4100) at the resolution rate of 4 cm⁻¹ to analyze the functional groups of phytochemicals.

2.4. DPPH scavenging assay

All the reagents used in the experiment were analytical grade. In this assay, 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical reduction through scavenging was performed according to the reported method with slight changes (Sengani et al., 2017). In brief, 1 mL of *S. trilobatum* leaf extract and AgNPs suspension with different concentrations, 100 µg/ml, 200 µg/ml, 300 µg/ml, 400 µg/ml and 500 µg/ml was aliquoted. Then added with an equivalent amount of 0.1 mM solution of DPPH in ethanol. The thoroughly mixed solution was incubated at ambient temperature for 30 min in the dark, the DPPH reduction was assessed by reading the absorbance at 517 nm using a spectrophotometer (Perkin-Elmer Lambda 40 UV/VIS). In his experiment, ascorbic acid (1 mM) was prepared as a standard reference and DPPH solution without sample solution was prepared for control.

2.5. Hydrogen peroxide radical scavenging assay

The *S. trilobatum* aqueous leaf extract and synthesized AgNPs were evaluated for hydroxyl radicals scavenging ability through the Fenton reaction (Deng et al., 2019). The reaction mixture was prepared by adding 0.2 M phosphate buffer about 2.4 mL (pH7.8), 1 mM FeCl₂ about 60 µl, 0.17 M H₂O₂ of about 150 µl, and 1 mM phenanthroline of about 90 µl. The reaction mixture incorporated with 1 mL of different concentration of *S. trilobatum* aqueous leaf extracts and AgNPs, 100 µg/ml, 200 µg/ml, 300 µg/ml, 400 µg/ml and 500 µg/ml. The reaction mixture was incubated for 5 mins at ambient temperature, absorbance was recorded at 560 nm using a UV spectrophotometer using ascorbic acid (1 mM) as a standard solution.

2.6. Estimation of the in -vitro anti-inflammatory activity through HRBC method

The 5 mL of whole blood was collected from the healthy human being with a heparinized vacutainer to avoid coagulation. Further, the tubes were centrifuged at 3000 rpm for 10–15 min. The supernatant was discarded, the pelleted packed RBC cells were suspended with an equal volume of normal saline (pH 7.4). The mixture was centrifuged, measured, and added with an equal volume of isotonic sodium phosphate buffer (10 mM, pH 7.4) solution. The heat-induced hemolysis was tested using the above solution. Sample were prepared in test tubes with increased concentration of plant extract (100 µg/ml, 200 µg/ml, 300 µg/ml, 400 µg/ml and 500 µg/ml), AgNPs (100 µg/ml, 200 µg/ml, 300 µg/ml, 400 µg/ml and 500 µg/ml) and diclofenac potassium (200 µg/ml) as standard (4 sets per dose). These sample tubes were added with 1 mL of sodium phosphate buffer (0.15 M, pH 7.4), 2 mL hypotonic saline, and 500 µl of HRBC suspension. The tubes were mixed thoroughly and were incubated at 56 °C for 30 min at a temperature-controlled water bath for 20 min. Further, the tubes were centrifuged and the supernatant examined for absorption spectra 560 nm (Helmy et al., 2020).

$$\text{Percentage membrane stability(\%)} \\ = 100 - \left(\frac{A_s - A_{c2}}{A_{c1}} \right) \times 100$$

where, A_s = Absorbance of standard and samples

A_{c1} and A_{c2} = Absorbance of control 1 and control 2, respectively.

2.7. The cyclooxygenase assays

The cyclooxygenase assays, including cyclooxygenase -1 and cyclooxygenase -2 were performed for different concentrations of *S. trilobatum* aqueous leaf extract and AgNPs with standard protocol (Jyoti et al., 2020). The COX-1 sample was prepared from seminal ram vesicles and COX-2 was prepared from human Prostaglandin H synthase isozymes-II by cloned with lysates of insects cell. Each reaction mixture contained with COX-1(10 μ l) and COX-2 (20 μ l) enzyme mixed with 1 mM phenol, 0.1 M Tris buffer (pH 7), 17 μ g of hemoglobin of about 600 μ l. The crude extract at different concentrations was made with DMSO and pre-incubated at 37 °C for 5 min with COX-I or COX-II enzymes. In addition to 1.64 μ M arachidonic acid in the reaction mixture, cyclooxygenase enzyme inhibition was initiated. The experiment evaluated O_2 uptake using O_2 electrode at 37 °C and IC_{50} values were calculated. The results are expressed as mean \pm standard error of two separate experiments and repeated twice.

3. Results

3.1. Synthesis and characterization of AgNPs

Silver nitrate ($AgNO_3$) synthesized into silver nano in addition to *S. trilobatum* aqueous leaf extract was observed immediately by reddish-brown, which was confirmed through UV-visible spectrum (Fig. 1). Thus, the absorption spectrum of AgNPs shows a well-defined exciton band near 430 nm. The average particle size measured through diffraction light scattering (DLF) is shown at 27.6 nm (Fig. 2A). In our study, the surface stability measured by zeta potential shows -39.2 mV (Fig. 2B). The XRD spectra have been recorded for dried AgNPs at 2θ angle and compared with the standard diffractogram in the Joint Committee on Powder Diffraction Standards (JCPDS) library. Also, spectra show (Fig. 3) four main peaks that match with the powdered diffraction standard values (hkl) of silver. The surface morphology was examined through HR-TEM, the images were taken at different magnifications shown in Fig. 4A, B, and C. The AgNPs were found to be spherical, the average particle size matching with our DLF results. The crystalline nature of AgNPs confirmed through the SAED pattern consisted of bright circular spots (Fig. 4D). The FTIR spectrum was recorded at $4000 - 400$ cm^{-1} (Fig. 5). The results showed that

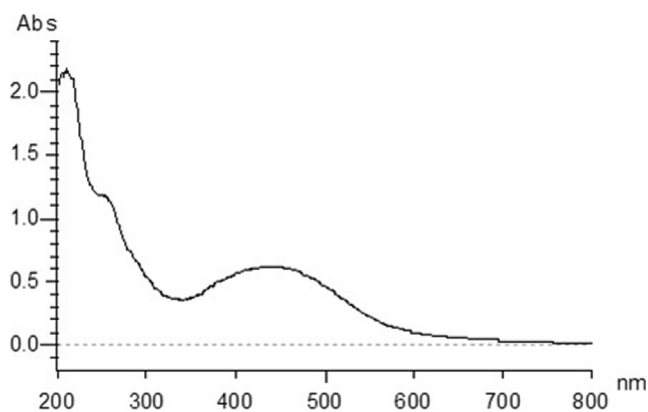


Fig. 1. UV-Visible spectrum of AgNPs using *Solanum trilobatum* aqueous extract.

broad absorption spectra for the hydroxyl group found between 3309.85 cm^{-1} confirm the involvement of diterpenes. Further, the sharp peak at 1606.70 indicates the presence of the phenyl group. The short sharp peak found at 1315.45 cm^{-1} indicates C (O)-O stretching vibrations and -OH in-plane vibrations/amide III compounds. The peak at 1031.91 cm^{-1} indicates the involvement of reducing sugars.

3.2. DPPH assay for antioxidant activity

The Free radical scavenging efficacy of plant extract and AgNPs were evaluated spectroscopically. The result is obtained and summarized in Table 1. Our findings reveal that the 76.10 μ g/ml of AgNPs and 126.16 μ g/ml of plant leaf extract were required to scavenge 50% of DPPH. When the concentration of leaf extract and AgNPs increases, the free radical scavenging activity also increases, respectively. Also, the AgNPs exhibited higher reducing power compared to the aqueous extract.

3.3. Hydrogen peroxide radical scavenging assay

The hydrogen peroxide radical scavenging assay results are shown in Table 2. About 95.36 μ g/ml of AgNPs and 130 μ g/ml of aqueous leaf extract were required to scavenge 50% of hydrogen peroxide. The scavenging power increased dose-dependently. *In-vivo* studies show that green synthesized metal nanoparticles could scavenge free radicals by predominantly catalase enzyme compared with others. At the same time, studies declared better antioxidant activity exhibited by AgNPs than the extract used for their synthesis (see Table 3).

3.4. In vitro anti-inflammatory activity by HRBC membrane stabilization assay

Inflammation is the tissue or organ injury resulting in symptomatic pain, swelling, temperature, and redness. Therefore, associated with membrane lipid peroxidation and several sequential pathological conditions. Therefore, regulation of lysosomal membrane damage is the rate-limiting step in minimalizing the inflammation. Several plant-derived compounds and their secondary metabolites mediate to synthesized nanoparticles which enhances the cell interactions to stabilize the cell membrane. The current study AgNPs and leaf extract showed that HRBC membrane stabilization and subsequently inhibit hemolysis in a dose-dependent manner is exhibited in Table 2. The anti-inflammatory activity AgNPs was found to be $68.24 \pm 2.1\%$ to $83.66 \pm 1.5\%$ when the HRBC cell was introduced into the hypertonic solution.

3.5. Cyclooxygenase 1 and 2 inhibition assay

The diverse secondary metabolites of *S. trilobatum* are reported, like steroids, triterpenoids, flavonoids, and tannins (Sahu et al., 2013). Further, the studies have shown that these metabolites and synthesized AgNPs promote the potential anti-inflammatory to inhibit the enzymatic activity of cyclooxygenase 1 and cyclooxygenase 2 was determined. The potential inhibition (IC_{50}) was evaluated to compare with the standard drug indomethacin. The results shown in Fig. 6 expressed that the AgNPs and aqueous leaf extract showed potential inhibition activity with isoforms of Cyclooxygenase 1 and 2. Besides, AgNPs were significantly inhibited the Cyclooxygenase 1 and 2 significantly high compared with aqueous leaf extract. The AgNPs expressed IC_{50} for 60.97 μ g/ml concentration and aqueous plant extract expressed IC_{50} for 65.97 μ g/ml concentration with COX-1. Similarly, AgNPs expressed IC_{50} for 62.37 μ g/ml concentration and aqueous plant extract expressed IC_{50} for 68.32 μ g/ml concentration with COX-2.

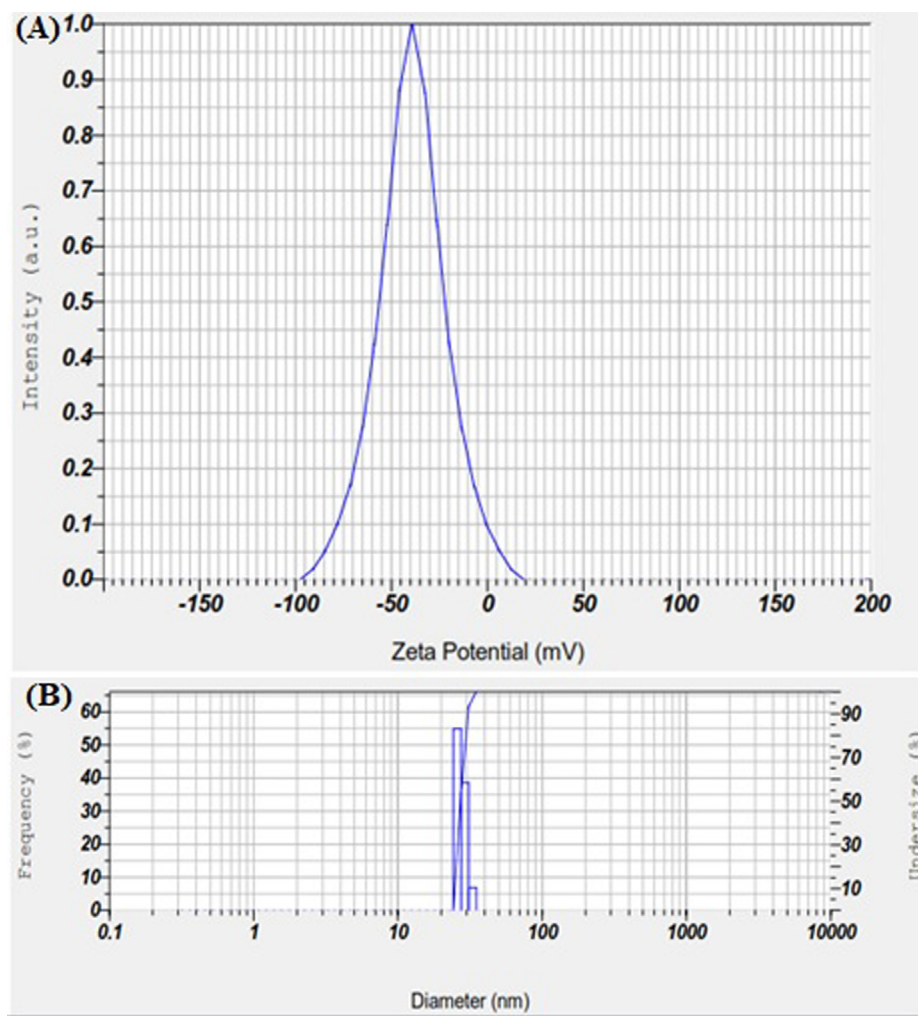


Fig. 2. (A) Particle size distribution histogram of AgNPs determined from DLS, (B) Surface charge of AgNPs measured from Zeta potential spectrum.

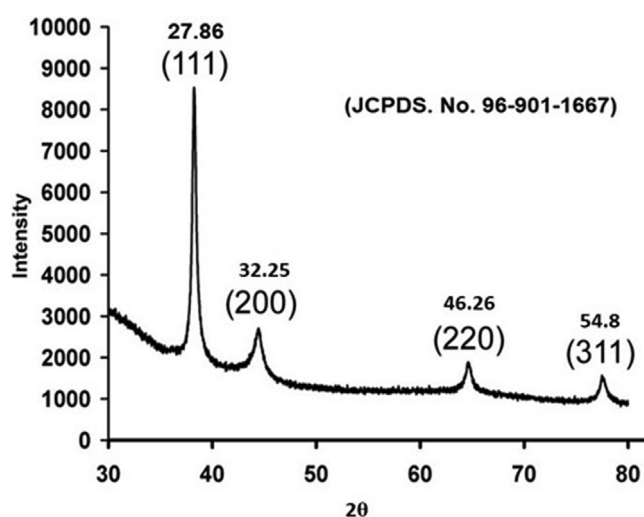


Fig. 3. X-ray diffraction pattern of synthesized AgNPs.

4. Discussion

The synthesized AgNPs were confirmed through the instant color change from pale yellow to brown clour, which had unique

optical properties resulting in strong light excitation, leading to the Surface plasmon resonance (SPR) phenomenon. The current study showed that the plant synthesized nanoparticles exhibit a negative charge due to the strong coordination of OH⁻ ions in plant polyphenols. Overall, the mixture of phytochemicals present in the herb contributes to the potential and synergistic effect toward various activities (Sim et al., 2004; Govindarajan and Benelli, 2016; Govindarajan et al., 2016a,b). Usually, these hydroxyl groups in the plant phenolic compound are associated with glycosylation, hydroxylation, and methoxylation. Thus, structural features are potentially intent with radical scavenging ability (Kharat and Mendhulkar., 2016). Frequently, the high potential elimination of Reactive oxygen species is the main barrier to these antioxidants.

Further, significant challenges in applying exogenous nanoparticles *in vivo* include adverse health effects due to mitochondrial respiration, oxidative stress, immune cell activation and genotoxicity. To overcome this, the hydrogen donating molecules from polyphenols, flavonoids, proteins, and terpenoids are present in the AgNPs act as stabilizers and reductants (Ovais et al., 2018). Thus, retain the antioxidant property and protects cells from various cellular damage caused by degenerative disorders, aging, and arthritis. These antioxidant radical scavenging activities protect from inflammations (Akhtar et al., 2017; Solano et al., 2020). Commonly, ionic silver molecules favor plasma membrane permeability and stimulate calcium ion channel modulation. Thus favors the entry of water and organic molecule into the cells (Klima

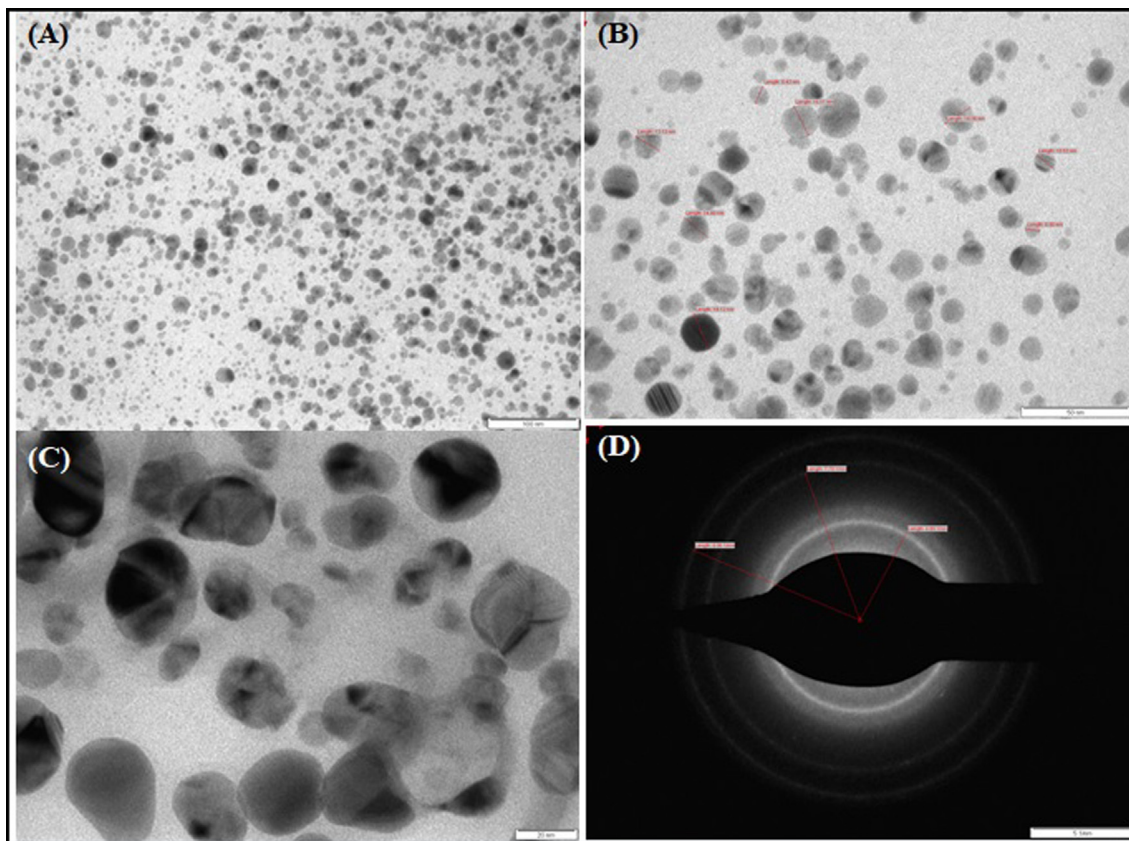


Fig. 4. HR-TEM micrograph images of synthesized AgNPs at different magnification scale (A) 100 nm, (B) 50 nm, (C) 20 nm and (D) SAED pattern.

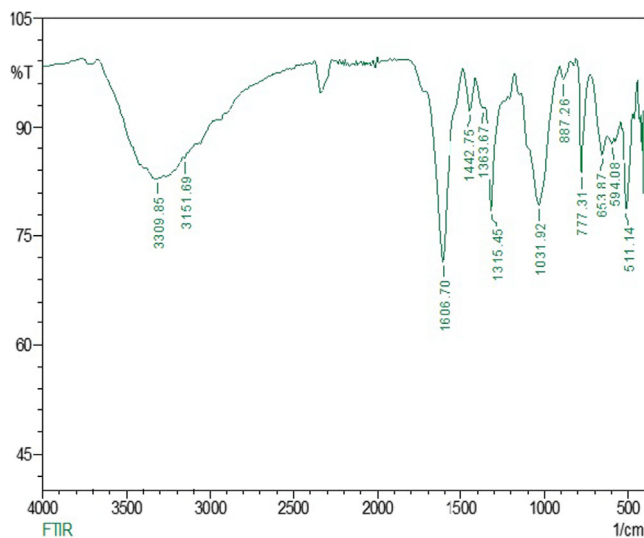


Fig. 5. FTIR spectra of synthesized AgNPs using *Solanum trilobatum* aqueous extract.

et al., 2018). Because, AgNPs were shown significant decreases in expression of cascade cyclooxygenase-1, 2 (COX-1, 2) gene and are supported in the inhibition of pro-inflammatory cytokines and similar Tumour Necrosis Factor- α (TNF- α) and Interleukins-12 (IL-12) production at higher concentrations (Das, 2011; Hussain et al., 2016). At the same time, COX 1 was inhibited more efficiently than COX2 by AgNPs and aqueous leaf extract. The studies showed that *S. trilobatum* leaf transcriptome initiates flavonoid biosynthesis in the plant, which highly contributes to the medicinal properties of these plants (Alagumanian et al., 2004).

Table 1
DPPH scavenging activity.

Concentration of $\mu\text{g/ml}$	% scavenging of standard	% scavenging of plant extract	% scavenging of AgNPs
20	48.73 \pm 0.3	21.56 \pm 0.4	30.6 \pm 0.4
40	58.32 \pm 0.6	26.14 \pm 0.5	42.8 \pm 0.6
60	61.56 \pm 0.5	29.52 \pm 0.3	49.5 \pm 0.3
80	64.42 \pm 0.2	32.05 \pm 0.4	52.56 \pm 0.8
100	73.24 \pm 0.4	39.63 \pm 0.8	60.4 \pm 0.5
IC ₅₀	34.29 $\mu\text{g/ml}$	126.16 $\mu\text{g/ml}$	76.10 $\mu\text{g/ml}$

Table 2
Hydrogen peroxide scavenging activity.

Concentration of $\mu\text{g/ml}$	% scavenging of standard	% scavenging of plant extract	% scavenging of AgNPs
20	68.14 \pm 1.4	18.50 \pm 1.2	28.16 \pm 0.9
40	72.32 \pm 1.3	26.44 \pm 0.6	32.82 \pm 1.2
60	75.10 \pm 0.5	33.42 \pm 1.5	46.21 \pm 0.8
80	78.36 \pm 1.9	36.10 \pm 0.4	48.56 \pm 0.6
100	82.24 \pm 1.2	38.32 \pm 1.3	52.43 \pm 1.3
IC ₅₀	14.67 $\mu\text{g/ml}$	130 $\mu\text{g/ml}$	95.36 $\mu\text{g/ml}$

Table 3
Anti-inflammatory effect of AgNPs and *Solanum trilobatum* and a standard on HRBC membrane haemolysis and stabilization.

Concentration of $\mu\text{g/ml}$	% inhibition of plant extract	% inhibition of AgNPs	% inhibition of diclofenac
5	67.48 \pm 1.56	68.24 \pm 2.1	85.61 \pm 1.30
10	67.32 \pm 2.60	69.38 \pm 1.8	87.46 \pm 3.60
15	74.15 \pm 2.40	76.72 \pm 2.4	88.45 \pm 1.40
20	77.36 \pm 3.20	79.58 \pm 1.6	90.60 \pm 2.10
25	82.14 \pm 1.80	83.66 \pm 1.5	92.46 \pm 1.60

Screening concentration for crude extracts was various from 5 to 25 $\mu\text{g ml}^{-1}$. Values are mean \pm SE of triplicates.

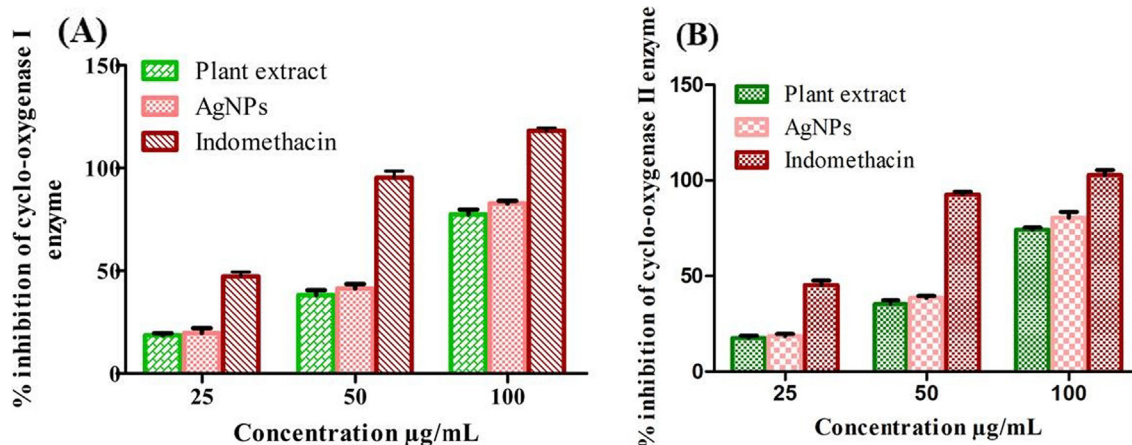


Fig. 6. Inhibition of human cyclo-oxygenase-I (COX-I) and cyclo-oxygenase-II (COX-II) by plant extract and AgNPs compared to standard. Values are expressed as mean \pm SEM; (n = 5).

5. Conclusion

The concept of nanoparticles synthesis using organic sources is a preferable alternative to chemical synthesis as eco friendly and it is less toxic for human health with nearly no adverse side effects. Our present study concluded that the antioxidant-rich bioactive metabolites in the plant extract and synthesized AgNPs significantly scavenged the free radicals. Further, the AgNPs showed a protective effect on HRBC membrane stability. Similarly, the study concludes that the silver nanoparticle shows efficient COX 1 and COX 2 inhibition comparatively with plant extract. Overall, the biosynthesized silver nanoparticles are being used as a potential alternative for inflammation instead of steroids and other immunosuppressant drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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