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APPENDIX

Appendix I

Sunlight mediated green synthesis of silver nanoparticles

(Mounil *et al.,* 2020 and Rautela *et al.,* 2019)

10 ml of the leaf extract was added to 90 ml of freshly prepared 1 mM silver nitrate solution to attain a final volume of 100 ml. Then it is kept under direct sunlight for 20 mins. Change in the color of the solution from brown to dark reddish brown indicates the reduction of Ag^{+} to Ag^{0}. The solution was then subjected to centrifugation at 15,000 rpm for 45 min. supernatant was discarded and the pellet that has silver nanoparticles was purified 4 times with deionized water for the removal of leaf extract residue and silver ions. After purification, the pellet was subjected to lyophilisation and stored in dark for further analysis

Appendix II

Preparation of silver nanoparticles loaded liposomes

(Fathy *et al.,* 2019)

The silver nanoparticles encapsulated liposomes were prepared using thin-film hydration method coupled with sonication. Cholesterol and phosphatidylcholine (Lecithin) were used at a molar ratio of 2:1. The mixture of cholesterol and lecithin was dissolved in 10 ml of chloroform until the formation of a clear solution. Using a rotary evaporator the chloroform was evaporated at 40ºC and then the flask was kept in vacuum overnight for the removal of the organic solvent completely which results in the thin lipid film formation. This thin film was then hydrated with the 5ml of silver nanoparticles dissolved in DMSO by placing it in a rotary evaporator for 5 mins. Thus obtained silver nanoparticles loaded liposomes were subjected to sonication to reduce the size of the liposomes. Then the non loaded silver nanoparticles present in the supernatant were removed by centrifugation.

Appendix III

Encapsulation efficiency of silver nanoparticles loaded liposomes

(Nayyer *et al.*, 2019)

The silver nanoparticle encapsulation efficiency was determined using the indirect spectrophotometric method. To determine the amount of silver nanoparticles encapsulated, the silver nanoparticles loaded liposomes were treated with chloroform and shaken well. This process releases the silver nanoparticles encapsulated in the liposomes which can be measured spectrophotometrically at 450 nm. The encapsulation efficiency can be calculated using the following formula

$$\text{Encapsulation Efficiency} = \frac{\text{Amount of Encapsulated Nanoparticle}}{\text{Amount of Encapsulated } + \text{Free Nanoparticle}} \times 100$$

Appendix IV

in vitro drug release study

(Kavithaa *et al.*, 2016)

The *in vitro* release of silver nanoparticles from the liposomes was analyzed using three different pH; pH 7.4 which corresponds to the pH of blood, pH 6.8 which corresponds to the pH of cancer cells, and pH 5.5 which corresponds to the mature endosomes of cancer cells. The *Tabebuia pallida* silver nanoparticles loaded liposomes were transferred to a dialysis bag. The dialysis bag was kept in 100 ml of phosphate-buffered saline at the various pH 5.5, 6.8, and 7.4 which is kept under a magnetic stirrer for continuous mixing of the contents to enable the uniform distribution of ions in the buffer. 5ml of the PBS solution was removed from the system and replaced with 5ml of fresh PBS solution at various time intervals like 2, 4, 8, 12, 24, 48, and

72 hours to determine the amount of silver nanoparticles released from the liposomes. The amount of silver nanoparticles released was estimated spectrophotometrically at 450 nm.

Appendix V

Application of *in vitro* drug release data on mathematical models

Several mathematical equations which generally define the dissolution profile. Once an appropriate function has been selected, the evaluation of dissolution profile can be carried out and hence the drug release profile can be correlated with drug release kinetic models. Various mathematical models are employed to understand drug release kinetics which is explained below.

Zero order model

According to the principles of pharmacokinetics, drug release from the dosage form can be represented by the equation:

$$C_t = C_0 + K_0 t$$

Where C_t – the amount of drug released at time t; C_0 - initial concentration of drug at time t=0; K_0- zero-order rate constant.

Thus, zero order kinetics defines the process of constant drug release from a drug delivery system and drug level in the blood remains constant throughout the delivery. Hence to study the drug release kinetics data obtained from in vitro dissolution study is plotted against time i.e., cumulative drug release vs. time. Hence the slope of the above plot gives the zero-order rate constant and the correlation coefficient of the above plot will give the information whether the drug release follows zero order kinetics or not. Thus, this model was applied in the release profile of silver nanoparticles loaded liposomes (Dash *et al.*, 2010)

First order model

The release of drug which follows first order kinetics can be represented by the equation

$$DC/dt = -K_1C$$

Where K1 is the first order rate constant, expressed in time^{-1} or per hour. Hence it can be defined as that in first order process, rate is directly proportional to the concentration of drug undergoing reaction i.e., greater the concentration faster the reaction. Hence, it follows linear kinetics. After rearranging and integrating the equation,

$$\log C = \log C_0 - K_1 t/2.303$$

where K_1 – first-order rate equation expressed in time^{-1} or per hour, C_0 is the initial concentration of the drug, C is the percent of drug remaining at time t

Hence to study the drug release kinetics data obtained from in vitro dissolution study is plotted against time i.e., log % of drug remaining vs. time and the slope of the plot gives the first order rate constant. The correlation coefficient of the above plot will give the information whether the drug release follows first order kinetics or not. Thus, this model was applied in the release profile of silver nanoparticles loaded liposomes (Dash *et al.,* 2010).

Higuchi model

The release of a drug from a drug delivery system (DDS) involves both dissolution and diffusion. Several mathematical equations models describe drug dissolution and/or release from DDS. In the modern era of controlled-release oral formulations, 'Higuchi equation' has become a prominent kinetic equation in its own right, as evidenced by employing drug dissolution studies that are recognized as an important element in drug delivery development. The Higuchi equation is considered one of the widely used and the most well-known controlled-release equation.

Higuchi equation can be represented in the simplified form

$$Q = K_H \times t^{1/2} \text{ where,}$$

Where K_H - Higuchi dissolution constant; Q – the cumulative amount of drug released in time t per unit area. Therefore the data obtained from *in vitro* drug release study can be plotted as cumulative percentage drug release versus square root of time. Hence if the correlation coefficient is higher for the above plot then we can interpret that the prime mechanism of drug release is diffusion controlled release mechanism. Thus, this model was applied in the release profile of silver nanoparticles loaded liposomes (Subal, 2006).

Korsmeyer-peppas model

Once it has been ascertained that the prime mechanism of drug release is diffusion controlled from Higuchi plot, and then it comes a question the release of drug follows which type of diffusion. To understand the dissolution mechanisms from the matrix, the release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas. Korsmeyer and Peppas put forth a simple relationship which described the drug release from a polymeric system follow which type of dissolution and he represented an equation as:

$$\log(M_t/M_\infty)=\log K_{kp}+n\log t$$

Where M_t – the amount of drug released in time t; M_∞ - the amount of drug released after time ∞; n- diffusional exponent or drug release exponent; K_{kp} - Korsmeyer release rate constant

To study release kinetics, a graph is plotted between log cummulative % drug release vs. log time. Hence, n value is used to characterize different release mechanisms. Thus, this model was applied in the release profile of silver nanoparticles loaded liposomes (Singhvi and Singh, 2011)

Hixson-crowell model

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles. Hence, particles of regular area are proportional to the cube root of its volume. From the above concept, Hixson-Crowell established a relationship between drug release and time which can be represented by equation

$$W0^{1/3}- Wt^{1/3}= K_{HC}{}^{t}$$

Where W_0- the initial amount of drug in the liposome; Wt is the remaining amount of drug in the liposome at time t; K_{HC}- Hixson-Crowell constant.

To study the release kinetics, a graph is plotted between cube root of percentage drug remaining in matrix versus time. Hence, if the correlation coefficient of the above equation is higher, then we can interpret that change in surface area during the process of dissolution has a significant effect on drug release. Thus, this model was applied in the release profile of silver nanoparticles loaded liposomes (Singhvi and Singh, 2011).

Appendix VI

DPPH Radical Scavenging Assay

Brand-Williams *et al.*, (1995)

Principle:

DPPH radical is scavenged by antioxidants through the donation of a proton forms the reduced DPPH. The color change from purple to yellow after reduction can be quantified by its decrease in absorbance at wavelength 520m.

Reagents

- DPPH – (2, 2-diphenyl-2-picryl hydrazyl hydrate) (0.1mM in methanol)
- Methanol
- Standard: Quercetin

Procedure

0.5 ml of 0.1mM DPPH solution in methanol was mixed with 0.5ml of hydroethanolic extract, silver nanoparticles and silver nanoparticles loaded liposomes of varying concentrations (25,50, 100,200, 300, 400 and 500 µg/ml). Corresponding blank was prepared and Quercetin (25-500µg/ml) was used as reference standard. Mixer of 0.5ml methanol and 0.5ml DPPH solution was used as control. The reaction was carried out in triplicate and the decrease in absorbance was measured at 520nm after 30 minutes in dark using UV-Vis spectrophotometer. The inhibition % was calculated using the following formula.

$$\text{Inhibition \%} = Ac\text{-}As/Ac \times 100$$

Where Ac is the absorbance of the control As is the absorbance of the sample

Appendix VII

ABTS radical scavenging assay

Shirwaikar *et al.*, (2006)

Principle:

ABTS is a chromogen which changes into a coloured mono cation radical form (ABTS+) in the presence of oxidative agent and has an absorption peak at 745 nm. Antioxidants reduce (ABTS+) into its colourless form and the extent of decolourisation is proportional to the percent reduction of (ABTS+)

Reagents

- 7mM ABTS - 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)
- 2.45mM Ammonium persulfate
- Ethanol
- Standard: Quercetin

Procedure

The ABTS radical cation (ABTS+) was produced by reacting ABTS solution (7mM) with (2.45mM) ammonium persulfate and the mixture was allowed to stand in dark at room temperature for 12 – 16 hours before use. 0.7ml ofhydroethanolic extract, silver nanoparticles and silver nanoparticles loaded liposomes of varying concentrations (25,50, 100,200, 300, 400 and 500 µg/ml) was added to 0.3mL of ABTS solution. Ethanol serves as the blank and ABTS in ethanol serves as the control. The absorbance (A) was read at 745nm and the percentage scavenging activity was calculated as follows,

% scavenging activity = Ac-As/Ac×100

Where Ac is the absorbance of the control As is the absorbance of the sample

Appendix VIII

Hydroxyl radical scavenging assay

Klein *et al.*, (1991)

Principle:

Hydroxyl radicals were generated from ferrous ammonium sulphate and EDTA. This was detected by their ability to react with ascorbic acid to produce yellow color complex which was measured at 412nm

Reagents

- Iron-EDTA
- 0.018% EDTA
- 0.85% DMSO
- 0.22% ascorbic acid
- 17.5% TCA
- Nash reagent: 75 g of ammonium sulphate, 3ml of glacial acetic acid and 2ml of acetyl acetone were mixed and make up to 1L with distilled water

Procedure:

Various concentrations (25,50, 100,200, 300, 400 and 500 µg/ml) of hydroethanolic extract, silver nanoparticles, silver nanoparticles loaded liposomes and standard quercetin were added to 1.0 mL of iron-EDTA solution, 0.5 mL of EDTA solution (0.018%), and 1.0 mL of DMSO (0.85% DMSO (v/v) in 0.1 M phosphate buffer, pH 7.4 sequentially. The reaction was initiated by adding 0.5 mL of ascorbic acid (0.22%) and incubated at 80–90 °C for 15 min in a water bath. After incubation the reaction was terminated by the addition of 1.0 mL of ice-cold TCA (17.5% w/v). 3 mL of Nash reagent was added and left at room temperature for 15 min. The reaction mixture without sample was used as control. The intensity of the colour formed was measured spectrophotometrically at 412 nm against reagent blank. The% hydroxyl radical scavenging activity was calculated by the following formula:

$$\% \text{ scavenging activity} = Ac\text{-}As/Ac \times 100$$

Where Ac is the absorbance of the control As is the absorbance of the sample

Appendix IX

Hydrogen peroxide scavenging activity

Ruch *et al.,* (1989)

Principle:

The hydrogen peroxide scavenging activity can be measured in terms of decrease in absorbance at 230nm spectrophotometrically.

Reagents:

- phosphate buffer (0.1 M, pH 7.4)
- 43mM H_2O_2 in phosphate buffer
- Standard: Quercetin

Procedure:

A solution of H_2O_2 (43 mM) was prepared in phosphate buffer (0.1 M, pH 7.4). 2.4ml of hydroethanolic extract, silver nanoparticles, silver nanoparticles loaded liposomes and standard quercetin of varying concentrations (25,50, 100,200, 300, 400 and 500 µg/ml) was added to 0.6 mL of H_2O_2 solution (0.6 mL, 43 mM). Blank solution was containing the sodium phosphate buffer without H_2O_2. The absorbance value of the reaction mixture was recorded at 230 nm and the percentage inhibition was calculated as follows,

% scavenging activity = Ac-As/Ac×100

Where Ac is the absorbance of the control: As is the absorbance of the sample

Appendix X

Reducing Power assay

Yıldırım *et al.*, (2001)

Principle:

The substances which have reduction potential react with potassium ferricyanide (Fe^{3+}) to form potassium ferrocyanide (Fe^{2+}), which then reacts with ferric chloride to form ferric–ferrous complex that has an absorption maximum at 700 nm.

Reagents:

- 0.2 M phosphate buffer , pH 6.6
- 1% potassium ferricyanide
- 10% TCA
- 0.1% ferric chloride
- Standard: Quercetin

Procedure:

Various concentrations (25, 50, 100,200, 300, 400 and 500 µg/ml) of hydroethanolic extracts, silver nanoparticles, silver nanoparticles loaded liposomes and standard quercetin were mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of potassium ferricyanide [K3Fe(CN)6] (1%), and then the mixture was incubated at 50°C for 30 min. Afterwards, 2.5 mL of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. Finally, 2.5 mL of the upper layer solution was mixed with 2.5 mL of distilled water and 0.5 mL of FeCl3 (0.1%), and the absorbance was measured at 700 nm. Increased absorbance of the reaction mixture indicates increased reducing power.

Appendix XI

Nitric oxide radical scavenging assay

Shirwaikar and Somashekar, (2003) and Sreejayan and Rao, (1997)

Principle:

Sodium nitroprusside in aqueous solution, at physiological pH, spontaneously generate nitric oxide, which interacts with oxygen to produce nitrite ions that is estimated spectrophotometrically at 546nm.

Reagents:

- 10mM sodium nitroprusside
- Griess reagent: 1% sulphanilamide, 2% ortho phosphoric acid and 0.1% naphthyl ethylenediamine dihydrochloride
- Phosphate buffer saline (0.025 M, pH 7.4)

Procedure:

Sodium nitroprusside (5 mM) in standard phosphate buffer saline solution (0.025 M, pH 7.4) was incubated with different concentration of hydroethanolic extracts, silver nanoparticles, silver nanoparticles loaded liposomes and quercetin (25, 50, 100,200, 300, 400 and 500 µg/ml) and the tubes were incubated at 25° C for 5 hr. After 5 hr, 0.5 ml of incubation mixture was removed and diluted with 0.5 ml of griess reagent. The absorbance of the chromophore formed during dizotization of nitrite with sulphanilamide and its subsequent coupling with naphthyl ethylene diamine was read at 546 nm and the percentage inhibition was calculated as follows,

$$\% \text{ scavenging activity} = Ac\text{-}As/Ac \times 100$$

Where Ac is the absorbance of the control As is the absorbance of the sample

Appendix XII

MTT dye reduction assay

Igarashi and Miyazawa (2001)

Principle

MTT is a water-soluble tetrazolium salt that is reduced by metabolically viable cells to a colored water insoluble formazan salt. Live cells convert MTT into its formazan derivative, the number of surviving cells can be determined by the amount of MTT formazan produced, which is measured in a microtiter plate reader.

Reagent

- PBS (Phosphate Buffer Saline) – pH-7.4
- MTT-3mg/ml in PBS
- Isopropanol in 0.04N HCl (acid-propanol)

Procedure

The treated Molt-3 cells and PBL were centrifuged and the medium was removed and then incubated with 50µl of MTT at 37ºC for 3 hours. After incubation, 200µl of PBS was added to all samples and the liquid was then carefully aspirated. Acid propanol of 200µl was added and left overnight in the dark. The absorbance was read at 650nm in a micro titer plate reader (Bio RAD, USA). The optical density of the control cells were fixed to be 100% viable and the percent viability of the cells in the treatment groups were calculated using the formula

$$\text{Percentage viability} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

Appendix XIII

Sulphorhodamine B assay

Skehan *et al*., (1990)

Principle

Sulphorhodamine B (SRB) is a bright pink aminoxanthene dye with two sulphonic acid groups. Under mild acidic conditions, SRB binds to protein basic amino acids in TCA fixed cells to provide a sensitive index of cellular protein content, which is directly proportional to cell viability. The SRB assay is useful in measuring drug-induced cytotoxicity.

Reagents

- TCA (40%, 1%)
- Sulphorhodamine B (SRB)- (0.4% in 1% TCA)
- Acetic acid (1%)
- Tris (10mM, pH 10.5)
- PBS

Procedure

After treatment with various treatment groups for 24 hours, Molt- 3 cells and PBL were collected by centrifugation and washed with PBS. An aliquot of 350µl of ice-cold 40% TCA was layered on the top of the treated cells and incubated at 4ºC for one hour after which they were washed 5 times with 200µl of ice cold PBS. The buffer was removed and SRB (350µl) was added to each tube and left in contact with the cells for 30 minutes at room temperature. The unbound dye was removed by washing four times with 350µl portion of 1% acetic acid. Then 350µl of 10mM Tris (pH 10.5) was added to each tube to stabilize the protein bound dye. The pellets were shaken gently for 20 minutes on a gyratory shaker. The debris was spun down and the absorbance of the tris layer in each group was transferred to a 96-well plate and read in a microtiter plate reader at 490nm. The optical density of the control cells were fixed to be 100% viabile and the percent viability of the cells in the treatment groups were calculated using the formula

$$\text{Percentage viability} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

Appendix XIV

Measurement of Apoptosis- Annexin V/FITC staining

Cell death was detected using Annexin V/FITC-PI apoptosis staining method by BD Mitoscreen kit (BD Biosciences, USA) using flow cytometry.

Principle:

The membrane loss integrity which escorts cell death in the last stage due to necrotic or apoptotic processes was preceded by Annexin V/FITC apoptosis staining technique. Hence, staining with vital dye Propidium Iodide (PI) along with FITC and Annexin V was used to identify the early apoptotic cells, late apoptotic cells and necrotic cells. The damaged and dead cells were permeable to PI whereas the live cells with intact membrane exclude PI.

Reagents

- Annexin V-FITC
- 10X Annexin V binding buffer (Dilute one part of 10X Annexin V into 9 parts of distilled water to make 1X working solution of Annexin V binding buffer)
- Propidium Iodide (PI)

Procedure:

The confluent Molt-3 cells and PBL were treated with different groups with an optimal dose and left undisturbed for 24 hours. After the incubation period, the cells were trypsinized and centrifuged at 10000rpm for 10 minutes and the supernatant was discarded. To the pellet 100µl of 1X Annexin V binding buffer was added and shuddered well. 5µl of Annexin V/FITC and 5µl of Propidium Iodide was used and stained for 15 minutes in dark at room temperature. 400µl of Annexin V binding buffer was added after the incubation period and mixed well. The cells were measured using BD FACSverse flow cytometer. The cell death mediated by apoptosis and changes accompanied by them were studied.

Appendix XV

Detection of Mitochondrial Membrane Potential (Δψ) by Jc-1 Staining

In whole cells the mitochondrial membrane potential was detected using BD Mitoscreen kit using flow cytometry.

Principle:

JC-1 (5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolcarbocyaninee iodide) is a lipophilic cationic fluorochrome. To evaluate the status of ΔΨ the membrane permeable lipophilic cationic chromosomes were used as probes of ΔΨ and that penetrates the cells and their fluorescence is a reflection of ΔΨ. JC-1 can exists in two different stages monomers and aggregates with different emission spectra at 527nm and 590nm respectively. It forms monomers at lower dye concentration and aggregations at higher dye concentrations.

Reagents:

- JC-1 dye (125µl of DMSO was added to the vial and stored at -20ºC)
- 1X assay buffer (diluted 10X assay buffer to 1X prior to use) Working solution: 12.5µl of the stock solution was taken and 1.2ml of 1X assay buffer was added to it and stored at 2º-8º C for 7days.

Procedure:

The treated Molt-3 cells and PBL were incubated for 24 hours. After the incubation period, the cells were trypsinized and centrifuged at 10000rpm for 10 minutes and the supernatant was discarded. To the pellet 0.5ml of JC-1 working solution was added and incubated for 10-15 minutes in a CO_2 incubator at 37ºC. After incubation the cells were washed with 2ml of freshly prepared 1X assay buffer and centrifuged for 5 minutes. Repeated the step and resuspended the pellets with 0.5ml of 1X assay buffer and analyzed within one hour using BD FACSverse. By the formation of monomers and J-aggregates we can differentiate the loss of mitochondrial membrane potential in the treatment group.

APPENDIX XVI

CELL CYCLE ANALYSIS

(Krishan, 1975)

Cell cycle analysis was carried out by flow cytometry, the distribution Molt-3 and PBL in various phases of the cell cycles was studied using PI stain (Krishan, 1975).

Principle:

The main aim of the cell cycle analysis is to focus on the mechanism which regulates the cell division and the timing and frequency of DNA duplication.

Reagents:

- RNase
- Sodium citrate
- Propidium Iodide (PI)
- Tween-20
- Distilled water (made up the solution to 100ml that can be stored for 6 months at 4ºC)

Procedure:

The different treatment groups were treated with an optimal dose and left undisturbed for 24 hours. After the incubation period, the cells were trypsinized and centrifuged at 10000rpm for 10 minutes and the supernatant was discarded. To the pellet 1ml of PI was added and stained in dark for 30 minutes. After the incubation period the stained cells were analyzed for the populations of G0/G1, S and G2/M phases of cell cycle using flow cytometry. The results obtained were analyzed using the software FACSuite (BD Bioscience, USA). It is mostly used to distinguish the distribution of cells in each stages of cell cycle and to identify at which stage the cells got arrested after treatment period.

Appendix XVII

Measurement of Reactive Oxygen Species (ROS)

(Cavalli *et al.*, 2012)

The major role of ROS in the current scenario is to act as a messenger in normal cell signal transduction, cell cycling, apoptosis, gene expression and also in the activation of signalling cascades. ROS can serve both as intra and extra cellular messenger.

Principle:

Due to oxidative stress there was an increased level of ROS generation which causes damage to lipids, proteins and DNA. When the level of ROS is lowered it helps in signalling molecules because of redox biology which maintains the physiological function. The level of ROS can be measured using flow cytometer.

Reagents:

- 1X binding buffer
- 2,7-dichlorofluorescein

Procedure:

The confluent cells were treated with the different treatment groups with an optimal dose and kept undisturbed for 24 hours. After treatment the cells were trypsinized and centrifuged at 10000rpm for 5 minutes and the supernatant was discarded. 100µl of 1X binding buffer was added to the pellet to resuspend the cells. The cells were stained using 5µl of 2,7-dichlorofluorescein for 15 minutes in dark. After the incubation period 500µl of 1X binding buffer was added to the stained cells and analyzed using BD FACS verse flow cytometry. It is mainly used to measure the levels of ROS production after treatment period. Due to the loss of mitochondrial membrane potential it causes more oxidative damage to the cancer cells and in turn induces more cell death.

PUBLICATIONS

- **Priyanka Jayachandran**, Suganya Ilango and Ramalingam Nirmaladevi (2021) Evaluation of Antioxidant Potential of Green Synthesized Tabebuia Pallida Silver Nanoparticles, *Journal of Advanced Scientific Research,* 12 (3) Suppl 1: 76-85.

- **Priyanka Jayachandran**, Suganya Ilango and Ramalingam Nirmaladevi (2021) In vitro free radical scavenging potential of Tabebuia pallida leaf extracts, *The Indian Journal of Nutrition and Dietetics,* 10-19.

- Suganya Ilango, **Priyanka Jayachandran,** Akshaya Sivaswamy, Udayadharshini Subaramaniyam, Sumithra Sukumar and Ramalingam Nirmaladevi (2022) Characterization and Anticancer Activity of Annona Muricata Leaf Fractions against T-Cell Acute Lymphoblastic Leukemia Cell Line (Molt-3), *Asian Journal of Organic & Medicinal Chemistry,* Vol. 7 No. 1.

- Suganya Ilango, **Priyanka Jayachandran** and Ramalingam Nirmaladevi (2021) In Vitro Antioxidant Activity of Annona Muricata Leaves, *Journal of Advanced Scientific Research,* 12 (1) Suppl 1: 32-41.

- Suganya Ilango**, Priyanka Jayachandran** and Ramalingam Nirmaladevi (2021) Isolation, Identification and Free Radical Scavenging Potential of Acetogenin Rich Fractions from Annona muricata Leaves, *The Indian Journal of Nutrition and Dietetics,* 81-91.

5a

List of Publication

S.No.	Title of the Paper	Journal Name	Remarks
1.	*in vitro* free radical scavenging potential of *Tabebuia pallida* leaf extracts	The Indian Journal of Nutrition and Dietetics	Indexed in UGC-CARE
2.	Evaluation of Antioxidant Potential of Green Synthesized *Tabebuia Pallida* Silver Nanoparticles	Journal of Advanced Scientific Research	Indexed in UGC-CARE
3	Isolation, Identification and Free Radical Scavenging Potential of Acetogenin Rich Fractions from *Annona muricata* Leaves	The Indian Journal of Nutrition and Dietetics	Indexed in UGC-CARE
4	*in vitro* Antioxidant Activity of *Annona muricata* Leaves	Journal of Advanced Scientific Research	Indexed in UGC-CARE
5	Epigenetic alterations in cancer	Frontiers in Bioscience, Landmark	Indexed in Scopus
6	Approaches for network based drug discovery	Frontiers in Bioscience-Scholar	Indexed in Scopus

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EVALUATION OF ANTIOXIDANT POTENTIAL OF GREEN SYNTHESIZED *TABEBUIA PALLIDA* SILVER NANOPARTICLES

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ABSTRACT

Plant mediated green synthesis of silver nanoparticles has gained much importance in the current scenario. In this study, *Tabebuia pallida* leaves were used as a reducing agent for the sunlight mediated green synthesis of silver nanoparticles. The formation of silver nanoparticles was confirmed by UV-Vis spectroscopy which exhibited absorption maxima at 450 nm which is the characteristic of silver nanoparticles. Further, the characterization of the silver nanoparticles were carried out using Fourier transform infrared spectroscopy analysis, Field Emission Scanning Electron Microscope, Dynamic Light Scattering, and X-ray diffraction analysis. The size of the synthesized silver nanoparticles was found to be ranging between 31.76 nm-50.36 nm and is spherical in shape. The crystalline nature of the synthesized nanoparticles was confirmed by x-ray diffraction. Furthermore, the green synthesized silver nanoparticles were evaluated for their free radical scavenging activity using DPPH Radical Scavenging assay, ABTS radical scavenging assay, Hydroxyl radical scavenging activity, Reducing Power assay and Nitric oxide radical scavenging assay compared with the standard antioxidant Quercetin. Green synthesized silver nanoparticles exhibited a higher antioxidant activity against all the tested free radicals. From this evidences, it could be concluded that the green synthesized *Tabebuia pallida* silver nanoparticles can be used as a potential antioxidant for pharmaceutical applications.

Keywords: Antioxidant Activity, *Tabebuia pallida*, Silver Nanoparticles, DPPH Radical Scavenging Activity, Free Radicals.

1. INTRODUCTION

Nanotechnology is one of the important disciplines of research in the current scenario. Plants and their derivatives are mainly employed in the synthesis of nanoparticles. Normally the size of the nanoparticles ranges from 1-100 nm [1]. Because of their high surface to volume ratio they possess very good mechanical, chemical and biological properties. Among the various metal nanoparticles synthesized including platinum, copper, gold, and cadmium, silver nanoparticles gained much importance because of their broad spectrum of applications [2].

There are many methods available for the synthesis of silver nanoparticles including radiation, electrochemical, photochemical methods and biological methods. Among these methods, sunlight mediated synthesis of silver nanoparticles gained much importance because this method leads to rapid synthesis of silver nanoparticles without the help of any instruments. In the field of nanoparticles synthesis, plants are employed and are widely accepted because they are devoid of toxic chemicals and the plants provide various secondary metabolites that act as capping agent and reducing agents which increase the stability of the nanoparticles [3, 4].

Antioxidants are very much important to protect the cells from any kind of degenerative reactions that are caused by free radicals. These antioxidant properties of the plants were attained by the presence of various secondary metabolites including phenols, flavanoids and terpenoids. According to the recent studies, inorganic nanoparticles including silver nanoparticles possess free radical scavenging potential. This might attribute to the various secondary metabolites involved in the reduction and capping of the silver nanoparticles during their formation [5].

Tabebuia pallida often called as "Pink trumpet tree" that belongs to the family "Bignoniaceae" is one of the largest genera that is distributed in South America, Central America and Western region of India [6] is the candidate plant of the current study to synthesize the silver nanoparticles.

The main aim of the present study is to carryout sunlight mediated green synthesis of silver nanoparticles from *Tabebuia pallida* and characterize by UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FTIR) analysis, Field Emission Scanning Electron Microscope (FESEM), Dynamic Light Scattering (DLS) and X-ray diffraction (XRD). Furthermore the green synthesized silver nanoparticles were evaluated for their free radical scavenging activity using DPPH Radical Scavenging Assay, ABTS radical scavenging assay, Hydroxyl radical scavenging activity, Reducing Power assay and Nitric oxide radical scavenging assay compared with the standard antioxidant Quercetin.

2. MATERIAL AND METHODS

2.1. Collection of Plant Species

Tabebuia pallida leaves from a place near Avinashi, Tirupur District, TamilNadu was used in the present study for analysis. The plant materials were cleaned many times with running tap water. Consequently the leaves were shadow dried and coarsely powdered, saved in a sealed container for further analysis in laboratory.

2.2. Authentication of Plant species

The plant was validated by the Botanical Survey of India [BSI], Southern Circle, Coimbatore. India. Authentication no: BSI/SRC/5/23/2019/Tech./193.

2.3. Extraction of the Plant Materials

10 g of the leaf powder was subjected to extraction in 100ml of hydro ethanol solvent (ethanol: water- 60:40) in a Soxhlet apparatus, filtered and stored for further use.

2.4. Synthesis of silver nanoparticles:

10 ml of the leaf extract was added to 90 ml of freshly prepared 1 mM silver nitrate solution to attain a final volume of 100 ml. Then it was kept under direct sunlight for 20 mins. Change in color of the solution from brown to dark reddish brown indicated the reduction of Ag^+ to Ag°. The solution was then subjected to centrifugation at 15,000 rpm for 45 min. Supernatant was discarded and the pellet that has silver nanoparticles was purified 4 times with deionized water for the removal of leaf extract residue and silver ions. After purification, the pellet was subjected to lyophilisation and stored in dark for further analysis [7, 8].

2.5. Characterization of synthesized silver nanoparticles

The synthesized silver nanoparticles were characterized by UV-visible spectroscopy (Shimadzu Bio Spec-nano), Fourier transform infrared spectroscopy analysis (FTIR spectroscopy- miracle 10, SHIMADZU), Field Emission Scanning Electron Microscope with EDAX (MIRA 3 TESCAN and EDAX APEX), Dynamic Light Scattering (Malvern Instruments, UK) and X-ray diffraction (X'pert Pro X-ray diffractometer).

2.6. Evaluation of Antioxidant Activity

2.6.1. DPPH Radical Scavenging Assay

Silver nanoparticles of *T. pallida* were analyzed for their free radical scavenging ability against DPPH radical as stated by the technique of Brand-Williams *et al.,* 1995 [9] with insignificant variations. 0.5 ml of 0.1mM methanolic DPPH solution was combined with 0.5 ml of plant extracts of various concentrations ranging from 25-500 µg/ml. Methanol without DPPH served as the blank and quercetin was used as standard. DPPH in methanol without the samples acted as control. The reaction composition was kept undisturbed for 30 mins in dark condition and later the absorbance was calculated at 520 nm with the help of UV-Vis spectrophotometer. The % scavenging was computed by applying the formula:

$$\% \text{ scavenging activity} = \{(Ac-As)/Ac\} \times 100$$

where Ac - control absorbance, As - sample absorbance

2.6.2. ABTS Radical Scavenging Assay

The antioxidant potential of the samples was determined by employing ABTS radical decolorization analysis as reported by Shirwaikar *et al.*, (2004) [10] with slight modifications. Equal volume of 7mM ABTS and 2.45mM Ammonium Persulfate was mixed 12-16 hours prior to use in dark condition at an ambient temperature. 0.7ml of sample of different concentration was allowed to react with ABTS solution (0.3 ml). The absorbance was calculated at 745nm and the percentage scavenging activity was computed as mentioned earlier.

2.6.3. Hydroxyl Radical Scavenging Activity

The hydroxyl radical scavenging ability of the samples was studied as reported by Klein *et al.,* (1991) [11]. Different concentrations of the samples were mixed with 1.0 mL of iron-EDTA, 0.5 mL EDTA, and 1.0mL of DMSO in 0.1 M phosphate buffer (pH 7.4) sequentially

0.5 mL of ascorbic acid was added to commence the reaction and the mixture was kept in a boiling water bath for 15 mins at a temperature of 80-90°C. Thereafter the reaction was terminated by adding 17.5% ice-cold TCA. Then 3mL of Nash reagent was included in the reaction mixture. After 15mins of incubation in an ambient temperature, the absorbance was calculated at 412 nm and the percentage scavenging activity was computed as mentioned earlier. A tube with all these reaction mixtures except the sample serves as the control.

2.6.4. Reducing Power Assay

The assay was carried as reported by Yıldırım *et al.,* (2001) [12]. Briefly, various concentrations of sample were combined with 2.5 mL of phosphate buffer (pH 6.6) and 2.5 mL of Potassium ferricyanide then the composition was kept at 50°C for 30 min. After 30 mins, 2.5mL of Trichloroacetic acid was added. Then the mixture was centrifuged at 3000 rpm for 10 min. Equal volume of supernatant and distilled water (2.5 ml) was mixed and 0.5 mL of $FeCl_3$ was added. The absorbance was calculated at 700 nm.

2.6.5. Nitric oxide Radical Scavenging Assay

The assay was carried out as reported by Shirwaikar and Somashekar, 2001 [13] and Sreejayan and Rao 1997 [14]. 5 mM SNP (Sodium nitroprusside) in 0.025 M PBS pH 7.4 was mixed with varying concentration of the samples and the reaction mixture was incubated at 25°C for 5 hrs. A tube with all these reaction mixtures except the sample served as the control and the buffer alone served as the blank. After 5 hrs of incubation, equal volume of reaction mixture and Griess reagent (0.5 ml) was mixed. The absorbance was calculated at 546 nm.

2.7. Statistical analysis

The radical scavenging assays were performed in triplicate and the values are represented as mean ± standard deviation. Statistical significance of the data was analyzed using one-way ANOVA by using Microsoft Excel, 2007 and P value < 0.05 was found to be statistically significant.

3. RESULTS AND DISCUSSION

3.1. Synthesis of silver nanoparticles

The plant extract of *Tabebuia pallida* was added to the aqueous solution of silver nitrate. After 20 mins of incubation in the direct sunlight, there was a rapid change in colour of the solution from brown to dark reddish brown which indicates the rapid reduction of Ag^+ to Ag^0 (Fig 1A and 1B). This color change is due to the Surface Plasmon Vibrations excitation in the synthesized silver nanoparticles [15].

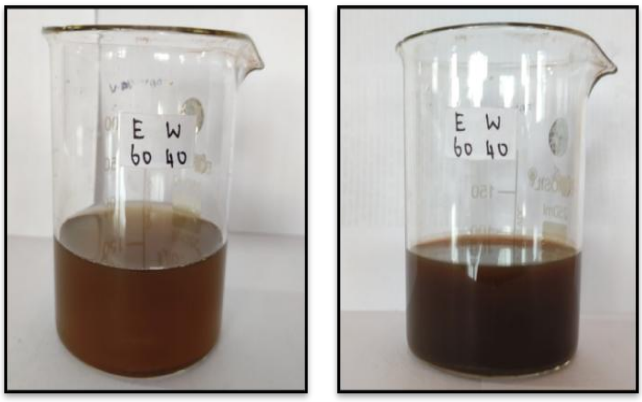


Fig. 1A **Fig. 1B**

Fig. 1A: Before exposure to sunlight, Fig. 1B: After exposure to sunlight for 20 mins

3.2. Characterization of synthesized silver nanoparticles

3.2.1. UV-Visible Spectroscopy

The silver nanoparticles synthesized using *Tabebuia pallida* leaf extracts were analyzed using UV-Vis spectroscopy to determine the characteristics of the peak spectrum of the silver nanoparticles. Normally the silver nanoparticles appear at the wavelength of 400-600 nm intervals [16]. The Surface Plasmon Resonance of the synthesized silver nanoparticles occur around 450 nm (Fig.2).

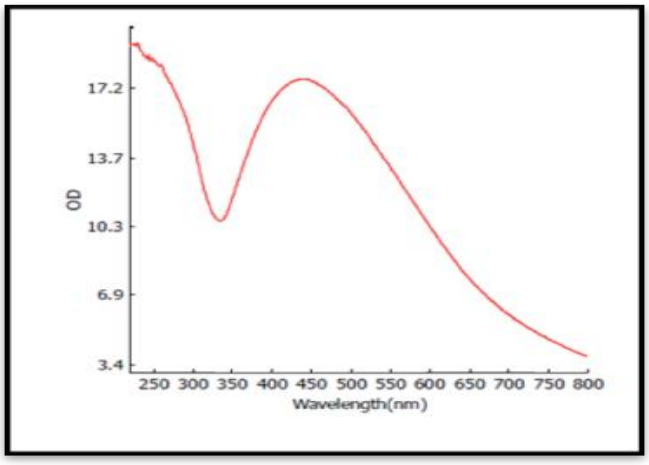


Fig. 2: UV-Visible spectrum of the synthesized silver nanoparticles

Little broadened and a bell shaped peak was formed due to the presence of various secondary metabolites in the plant extract that plays a major part in capping and

reducing mechanism during the formation of silver nanoparticles [17]. According to a theory postulated by Mie, the nanoparticles that are spherical in nature exhibit a single SPR peak. Thus from the above UV-Vis spectrum it is confirmed that the green synthesized silver nanoparticles are spherical in nature [18, 19]. In line with our study Pirtarighat *et al.* (2019), synthesized the silver nanoparticles using the plant extract of *Salvia spinosa* and found that the Surface Plasmon Resonance of the synthesized nanoparticles was at 450 nm [20].

3.2.2. Fourier Infrared Spectroscopy Analysis

The metabolites that play a key role in the reduction of silver ions were identified using FTIR spectroscopy. FTIR spectrum of the green synthesized *Tabebuia pallida* silver nanoparticles is shown in the fig.3. Various peaks in the FTIR spectrum corresponds to the functional groups of various metabolites involved in the reaction. A band at 601.79 cm^{-1} corresponds to the C-Cl (alkyl halides). Another band at 678.94 cm^{-1} indicates the presence of =CH of aromatic compounds present in the nanoparticles. A peak at 2360.87 cm^{-1} corresponds to the symmetric stretching of COO- [21]. Another peak at 1643.35 cm^{-1} indicates the amide-I from the carbonyl stretch in the amide linkage of proteins [22]. Various peaks at 3865.35 cm^{-1}, 3741.90 cm^{-1} and 3286.70 cm^{-1} correspond to the hydroxyl (OH) stretching vibration of the alcohol and phenols in the synthesized silver nanoparticles [23].

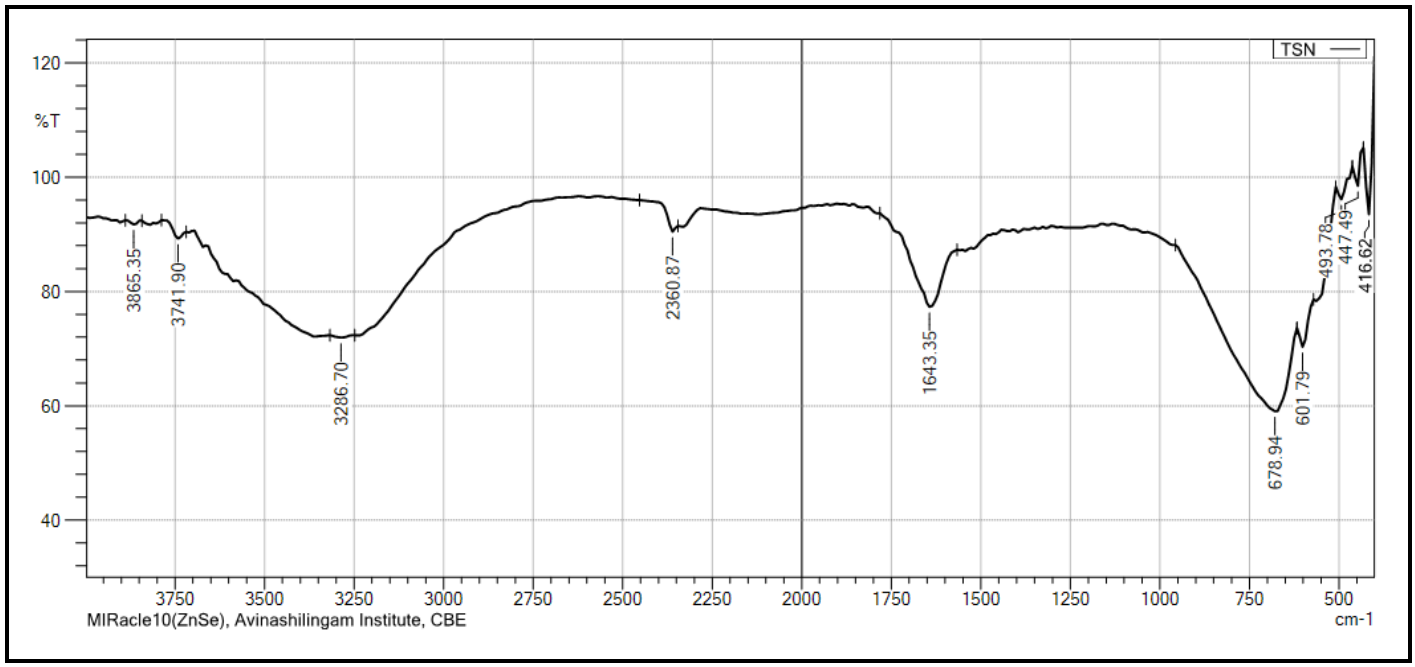


Fig. 3: FTIR Spectrum of synthesized silver nanoparticles

3.2.3. FESEM analysis with EDAX

FESEM analysis of the green synthesized *Tabebuia pallida* silver nanoparticles was carried out to analyze the morphology and size. The synthesized nanoparticles were found to be uniformly spherical in shape with the size ranging between 31.76 nm-50.36 nm with least agglomeration and the average size is found to be 38.82 (Fig.4). This difference in particle sizes is due to the involvement of various biomolecules in the synthesis and capping of silver nanoparticles [24]. Similar results were also obtained by Sathishkumar *et al.,* (2012) in the silver nanoparticles synthesized from *Morinda citrifolia*. They found that the size of the synthesized nanoparticles ranges between 10 to 60 nm and the average size is found to be 27nm [25].

The energy dispersive spectrum of the green synthesized *Tabebuia pallida* silver nanoparticles is depicted in the fig.5 A. A strong peak at 3 KeV indicates the silver nanoparticles because of their Surface Plasmon Resonance [26]. Various elements like Ag, Cl, C, and O are present in the synthesized nanoparticles and their percentage weight is 65.94, 3.52, 15.46, and 15.08 respectively (Fig.5 B). This is one of the biggest advantages over the nanoparticles which are synthesized chemically.

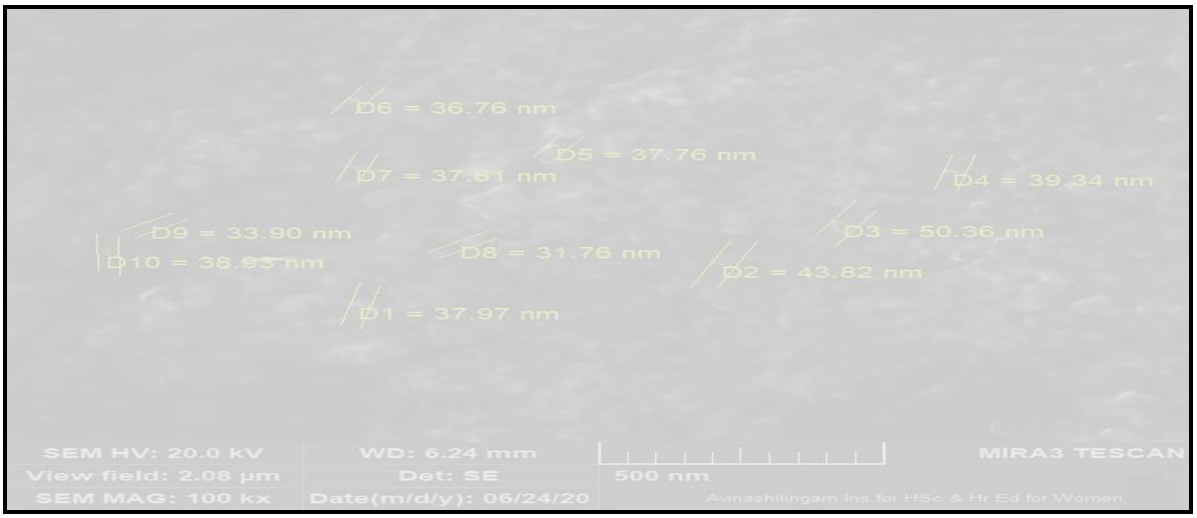


Fig. 4: FESEM Analysis of the synthesized silver nanoparticles

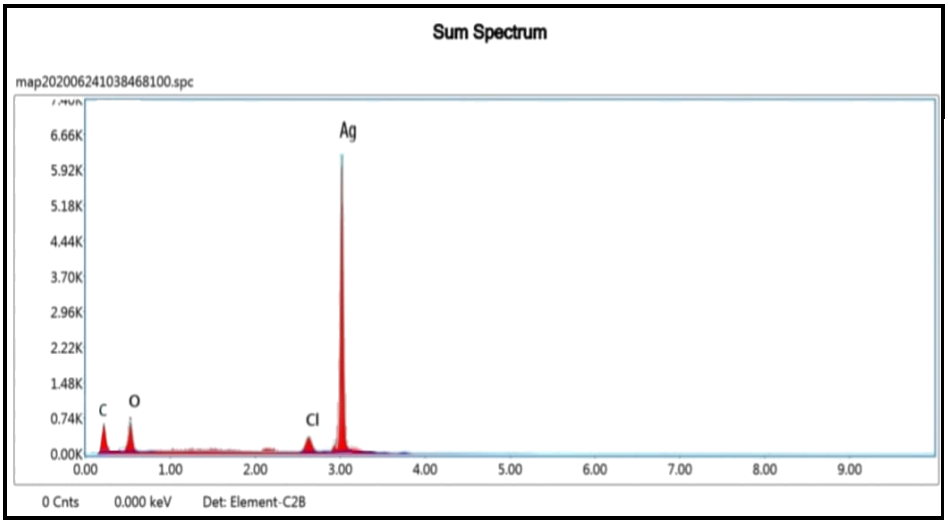


Fig. 5A

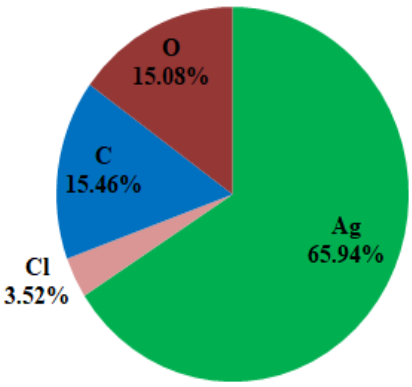


Fig. 5B

Fig. 5A: Energy dispersive spectrum of the silver nanoparticles, Fig. 5B: % weight of various elements in the synthesized silver nanoparticles

3.2.4. DLS analysis for particle size and zeta potential

DLS analysis was carried out to determine the particle size, particle distribution index and Zeta potential of the synthesized silver nanoparticles. It is observed that the average size of the nanoparticles was 55.4 nm with a Polydispersity Index (PDI) of 0.33. A single peak obtained in the DLS indicates the purity of the synthesized nanoparticles (Fig. 6A). This obtained size is slightly greater than the size obtained in SEM analysis. This is due to the fact that the SEM only measures the number based size distribution of the physical size and it will not include the capping agent. But the DLS is based on the measurement of hydrodynamic size which measures diameter of the particle along with the molecules and ions that are attached on the surface of the particle and are in continuous movement in the solution. This makes the size little lager in DLS than SEM [27].

The Zeta potential of the green synthesized silver nanoparticles was found to be -15.6 mV (Fig. 6B). This negative value is due to the presence of negative charge on the outer surface and positive charge on the inner surface of the nanoparticles. From this negative zeta potential it could be confirmed that the synthesized silver nanoparticles were stable for a longer duration since there will be a strong repulsion among the particles that prevents them from agglomeration [28].

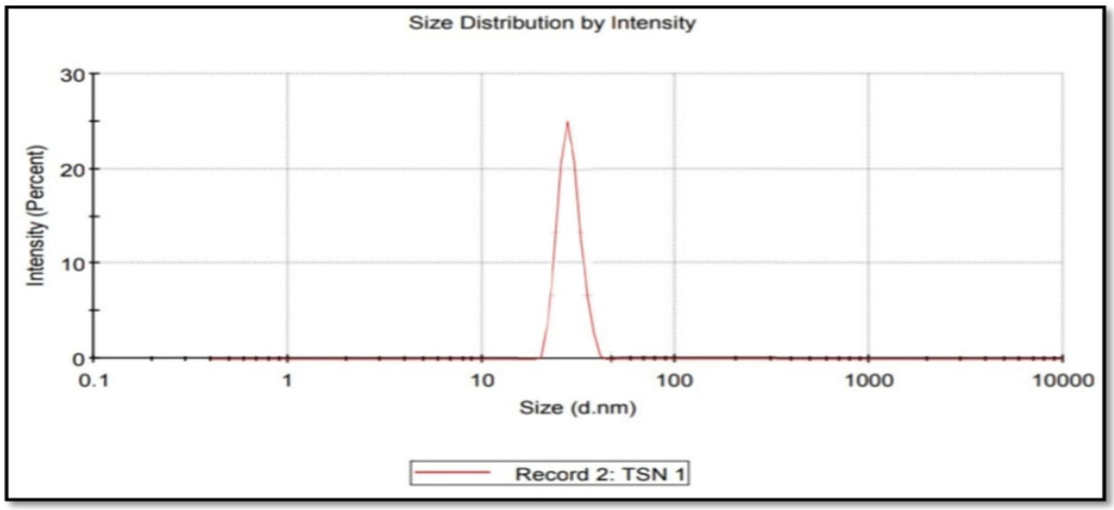


Fig. 6A: DLS spectrum of size distribution for the synthesized nanoparticles

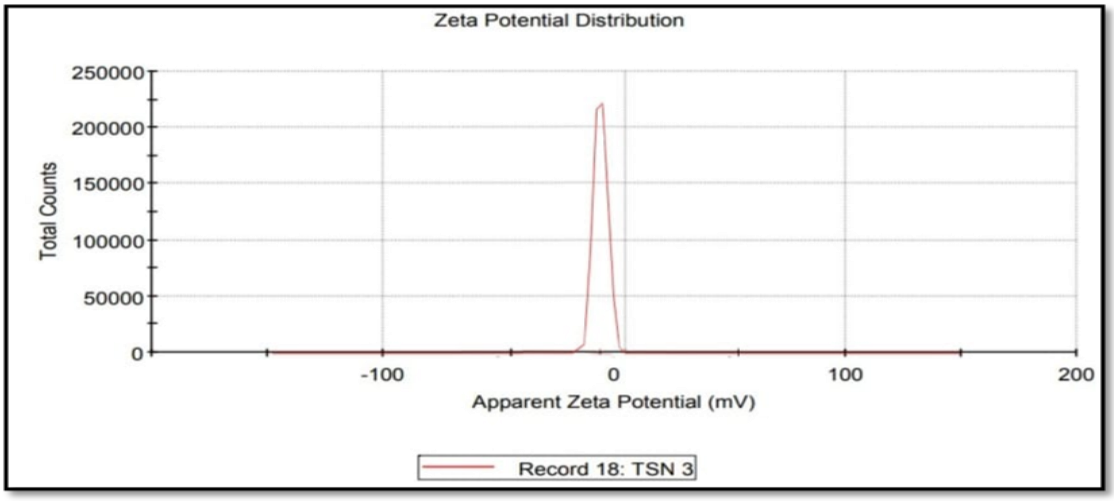


Fig. 6B: Zeta potential distribution of the synthesized silver nanoparticles

3.2.5. XRD Analysis

XRD analysis plays a major role in the characterization of the nanoparticles for identifying the structure and crystalline nature of the particle. The XRD pattern of the green synthesized *Tabebuia pallida* nanoparticles shows various diffraction peaks at 2θ = 32.20, 38.08, 46.18, 54.80 corresponds to the (111), (200), (120) and (202) planes respectively (Fig. 7A and 7B). These diffraction patterns indicate the presence of face centered cubic crystalline structure of the synthesized nanoparticles. Our results very well coincide with Hemlata *et al.,* (2020) who carried out biosynthesis of silver nanoparticles Using *Cucumis prophetarum* aqueous leaf extract [29]. The other peaks at 2θ = 21.60, 27.82 and 57.47 are the biomolecules present in the nanoparticles as a capping agent [30].

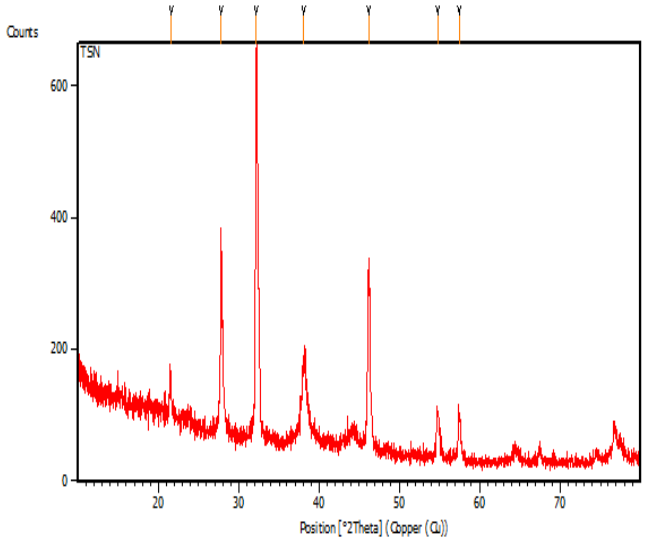


Fig. 7A

S.No.	Pos. [° 2Th.]	Height [cts]
1	21.6039	33.36
2	27.8273	300.69
3	32.2066	580.30
4	38.0854	124.06
5	46.1882	262.71
6	54.8036	67.08
7	57.4705	68.09

Fig. 7B

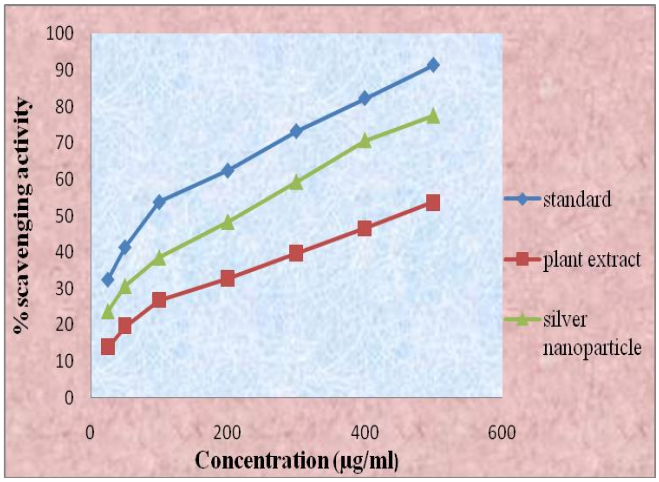
Fig. 7A: XRD diffraction pattern of the synthesized silver nanoparticles, Fig.7B: 2θ position and height of the spectrum

3.3. *In-vitro* Free Radical Scavenging Assays

3.3.1. DPPH Radical Scavenging Assay

The DPPH scavenging ability of the antioxidants is mainly due to the donation of hydrogen bond to the free radical. The plant phytochemicals like terpenoids, flavonoids, phenols and other phytoconstituents in the synthesized silver nanoparticles as a capping agent plays a major role in the scavenging of DPPH radicals. Initially the DPPH solution was purple in color and when exposed to the nanoparticles, it turns yellow due to acceptance of hydrogen. This clearly indicates the scavenging potential of the synthesized nanoparticles against DPPH [31]. The results of the DPPH scavenging ability of synthesized silver nanoparticles and *Tabebuia pallida* leaf extract are comparable with that of the standard quercetin is shown in the graph below (Fig. 8). From the graph it could be concluded that DPPH scavenging ability increases with increase in concentration of the AgNPs, Plant extract and quercetin. Notably, AgNPs exhibited highest scavenging ability of 77.63% in its highest concentration i.e. 500 µg/ml, whereas the plant extract and quercetin exhibited 53.77% and 91.52% scavenging potential in the same concentration. The IC_{50} value of the silver nanoparticles and plant extract was found to be 227.82 µg/ml and 439.23 µg/ml and IC_{50} for quercetin was 118µg/ml.

Our results are in accordance with the previously published results of Arumugam *et al.,* who carried out green synthesis of silver nanoparticles from *Lippia nodiflora* aerial extract and found that the DPPH scavenging ability was found to be increased with increase in concentration of the sample. AgNPs showed highest scavenging of 67% at 500 µg/ml and the standard exhibited 83% scavenging at the same concentration [32].



The values are represented as ±SD for triplicates in each category, P value < 0.05

Fig. 8: DPPH radical scavenging activity of the silver nanoparticles

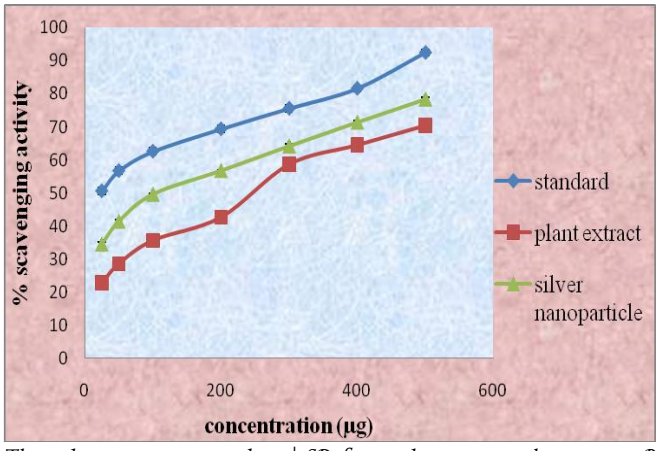
3.3.2. ABTS radical scavenging assay

ABTS radical scavenging assay was mainly used to determine the radical scavenging ability of both chain-breaking and hydrogen ion donating antioxidants [33]. The ABTS scavenging ability of the AgNPs and Quercetin was expressed in the graph (Fig.9). The ABTS scavenging ability was increased with increase in concentration of both samples and standard. The scavenging ability of AgNPs was 34.64- 78.47% at a concentration range of 25-500 µg/ml, for standard it was 50.56- 92.39 % and for the plant extract it was 22.77- 70.54 % in the same concentration. The IC_{50} value was found to be more for the AgNPs (148.23 µg/ml) and plant extract (264.3µg/ml) and is comparatively less for the standard (24.56 µg/ml). In line with our study pooja *et al.,* synthesized silver nanoparticles using *Cassia roxburghii* leaf extract and found that the scavenging ability was increased with increase in concentration of the sample and achieved a highest scavenging potential of 73% in its highest concentration [34].

3.3.3. Hydroxyl radical scavenging activity

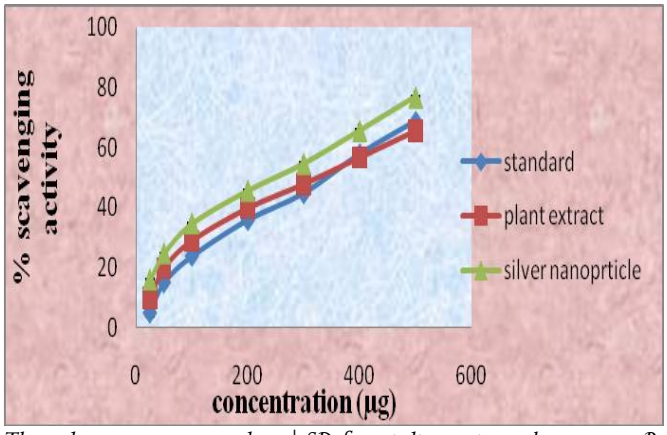
The hydroxyl radical scavenging activity of the synthesized silver nanoparticles, plant extract and standard quercetin was expressed in the Fig.10. The hydroxyl radical scavenging potential of the AgNPs is mainly due to the phenolic compounds that are responsible for the reduction of silver ions [35]. In our study, it was found that the hydroxyl radical scavenging potential increases with increase in concentration of the

sample. The hydroxyl radical scavenging potential of the AgNPs (76.78% at a concentration of 500µg/ml) was found to be higher than that of the standard quercetin (68.70% at a concentration of 500µg/ml) whereas the plant extract showed 65.62% scavenging effect against hydroxyl radicals. The IC_{50} value of AgNPs was found to be 264.78µg/ml and for the standard it was 339.27µg/ml. These results indicate that the hydroxyl radical scavenging ability of the AgNPs was very strong when compared to that of the standard quercetin. Our study was supported by a study carried out by Anand *et al.,* who synthesized silver nanoparticles from *Cestrum nocturnum* and carried out hydroxyl radical scavenging activity and found that the hydroxyl radical scavenging potential of the synthesized silver nanoparticles was found to be higher than that of the standard [36].



The values are represented as ±SD for triplicates in each category, P value < 0.05

Fig. 9: ABTS radical scavenging activity of the silver nanoparticles

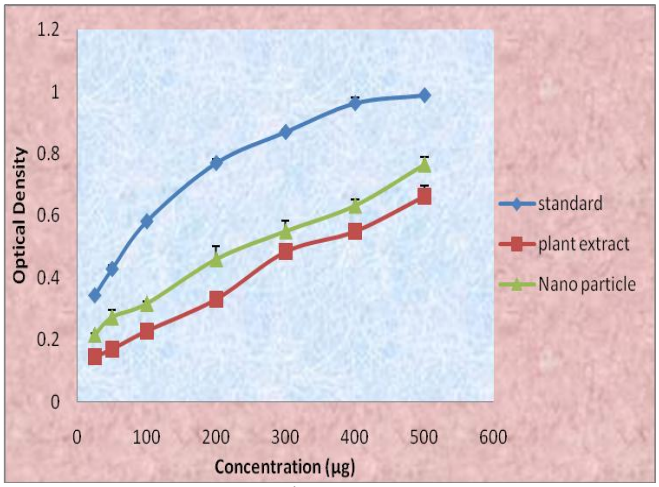


The values are represented as ±SD for triplicates in each category, P value < 0.05

Fig. 10: Hydroxyl radical scavenging activity of the synthesized silver nanoparticles

3.3.4. Reducing Power assay

The compounds which have the reducing ability will react with potassium ferricyanide and convert it to potassium ferrocyanide, this potassium ferrocyanide then reacts with ferric chloride and produces ferric-ferrous complex which can be measured at 700nm [37]. In the present study, it was found that the reducing power of plant extract, silver nanoparticle and the standard increases with increase in concentration (Fig. 11). The reducing ability of the standard quercetin was higher when compared to the AgNPs and plant extract. In line with our study Bhakya *et al.*synthesized silver nanoparticles from *Helicteres isora* and carried out various antioxidant assays. From their study it was found that the reducing ability of both standard and silver nanoparticles increases with increase in concentration [38].



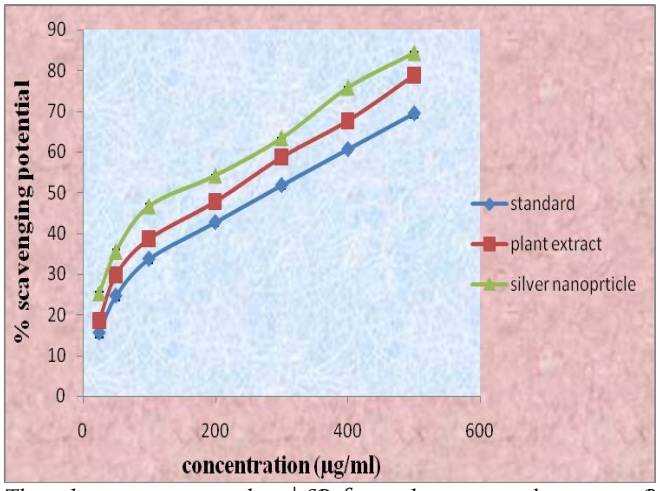
The values are represented as ±SD for triplicates in each category, P value < 0.05

Fig. 11: Reducing power assay for the synthesized silver nanoparticles

3.3.5. Nitric oxide radical scavenging assay

Increased production of nitric oxide in the body leads to several disease complications [39]. So, excess nitric oxide should be scavenged by the antioxidants to maintain a healthy homeostasis. In our study, it was found that the nitric oxide radical scavenging ability increases with increase in concentration (Fig.12). The scavenging ability of AgNPs was 25.33%- 84.33% at a concentration range of 25-500 µg/ml, for plant extract it was 18.57%- 78.77% and for standard it was 15.51 %- 69.45 % in the same concentration. The IC_{50} value was found to be less for the AgNPs (181.49 µg/ml) and comparatively more for the standard (295.71µg/ml).

Our study was supported by Rajeshwari *et al* who carried out nitric oxide assay for the green synthesized silver nanoparticles from *Aegle marmelos* leaf extract and found that the scavenging potential of silver nanoparticles increases with increase in concentration [40].



The values are represented as ±SD for triplicates in each category, P value < 0.05

Fig. 12: Nitric oxide radical scavenging ability of the synthesized silver nanoparticles

4. CONCLUSION

Sunlight mediated green synthesis of silver nanoparticles was carried out using *Tabebuia pallida* leaf extract. The color change of the reaction mixture indicates the formation of silver nanoparticles. The synthesized silver nanoparticles were further characterized by UV-visible spectroscopy, Fourier transform infrared spectroscopy (FTIR) analysis, Field Emission Scanning Electron Microscope (FESEM), Dynamic Light Scattering (DLS), x-ray diffraction (XRD). The surface Plasmon resonance of the synthesized silver nanoparticles in UV-visible spectroscopy occur around 450 nm which is the main characteristic of the silver nanoparticles. FTIR spectral studies showed the presence of various functional groups of secondary metabolites which acted as a reducing and capping agent in the mechanism of silver nanoparticles synthesis. FESEM along with EDAX indicates that the average size of the synthesized nanoparticles is around 38.82 nm and is uniformly spherical in shape with very less agglomeration and the percentage weight of Ag was found to be 65.94. In DLS analysis it is observed that the average size of the nanoparticles was 55.4 nm with a Polydispersity Index (PDI) of 0.33 and the zeta potential was found to be -15.6 mV. XRD analysis confirms that the synthesized nanoparticles are face centered cubic crystalline structure compared with the standard powder diffraction card. Furthermore the green synthesized silver nanoparticles were evaluated for their free radical scavenging activity using DPPH Radical Scavenging Assay, ABTS radical scavenging assay, Hydroxyl radical scavenging activity, Reducing Power assay and Nitric oxide radical scavenging assay compared with the standard antioxidant Quercetin. The silver nanoparticles, plant extract and standard quercetin exhibited a dose dependent scavenging potential

5. ACKNOWLEDGEMENTS

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Conflict of interest

None declared

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In vitro free radical scavenging potential of *Tabebuia pallida* leaf extracts

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Abstract

Plants are the reservoir of various phytochemicals that gives more health benefits to the human body. They are widely used by our ancestors in traditional folk medicine. The major advantage of these phytochemicals is that they can be used to cure various diseases with little or no side effects. Free radicals play a major role in various disease conditions by causing damage to the cells. Antioxidants contribute an extensive part in defending the cells against damage and reduce the deleterious consequence of the free radicals mediated increased oxidant production. Plants contain a number of enzymic and non-enzymic antioxidants which render a better effect against these ailments. The main objective of the present study is to nalyse the antioxidant potential of various solvent extracts of Tabebuia pallida leaf. Free radical scavenging assays like, "DPPH, ABTS, hydroxyl radical, reducing power and nitric oxide assays", for the various solvents ``methanol, ethyl acetate, benzene, ethanol, chloroform, petroleum ether, acetone and water" of the leaf extracts of Tabebuia pallida were performed. All the extracts tested exhibit a remarkable radical scavenging effect as the concentration increases. So these antioxidant compounds from plant origin can be used as an alternative for the synthetic antioxidants that are available in the market.

Keywords: *phytochemicals, Tabebuia pallida, free radicals, antioxidants, DPPH*

Introduction

Phytonutrients which are commonly known as phytochemicals are naturally available biologically active compounds present in the variety of plant species which exerts a specific biological role that improves human health. More than 10,000 phytochemicals exist in nature but only very less have been isolated and characterized[1,2]. Some of the well known phytonutrients from plants include flavonoids, catechins, saponins, isoflavones, phenolic acids, carotenoids and anthraquinones[3,4].

Free radicals contain unpaired electrons in their atomic orbital that exists independently. Some of the important radicals that leads to various ailments includes $O_2^{\bullet -}$, NO radical, hydrogen peroxide, $^{\bullet}OH$ and oxygen singlet. These free radicals in excess disturb the macromolecules of the body leading to cellular damage which finally results in diseased condition. These free radicals normally target various macromolecules including proteins, nucleic acids and lipids[5].

Antioxidants also known as free radical scavengers are the substances that inhibit oxidation[6]. In contemporary natural antioxidants of plant emergence gained much importance since they do not produce any adverse effects compared to the antioxidants synthesized in industries. Herbs, vegetables, seeds, spices and fruits are the natural sources of these antioxidants. These antioxidants are liked by most of the researchers not only because of their biological significance and also due to their economic impact[7].

Tabebuia palllida often called as "Pink trumpet tree" that belongs to the family "Bignoniaceae" is one of the largest genera that is distributed in South America, Central America and Western region of India[8] is the candidate plant of the current study. The free radical scavenging ability of the various extracts of *Tabebuia palllida* has been analyzed in this study.

Materials and Methods

Collection of plant species

Tabeubia pallida leaves were gathered from a place near Avinashi, Tirupur District, Tamil Nadu. The plant materials were cleaned many times with running tap water. Consequently the leaves were shadow dried and coarsely powdered, stored in a sealed container for further analysis in the laboratory.

Authentication of plant species

The plant was validated by the Botanical Survey of India, Southern Circle, Coimbatore with the Authentication no: BSI/SRC/5/23/2019/Tech./193.

Chemicals

All the chemicals employed in the current study were of analytical class.

Extraction of the plant materials

A 10 g of the leaf powder was subjected to extraction in 100 ml of different solvents of varying polarity, "methanol, ethyl acetate, benzene, ethanol, chloroform, petroleum ether, acetone and water" in a Soxhlet instrument. The solvents present in gathered extracts were reduced in a boiling water bath, stored and then used for further analysis after dissolving in dimethyl sulfoxide DMSO.

DPPH radical scavenging assay

Various extracts of *T. pallida* were analyzed for their free radical scavenging

ability against DPPH radical as stated by the technique of Brand-Williams *et al*[9] with insignificant variations.

ABTS radical scavenging assay

The antioxidant potential of the various solvent extracts of *T. pallida* was determined by employing ABTS radical decolorization analysis as reported by Shirwaikar *et al*[10].

Hydroxyl radical scavenging activity

The hydroxyl radical scavenging ability of the *T. pallida* leaf samples was studied as reported by Klein *et al*[11].

Reducing power assay

The reducing ability of various extracts of *T. pallida* was studied as reported by Yıldırım *et al*[12].

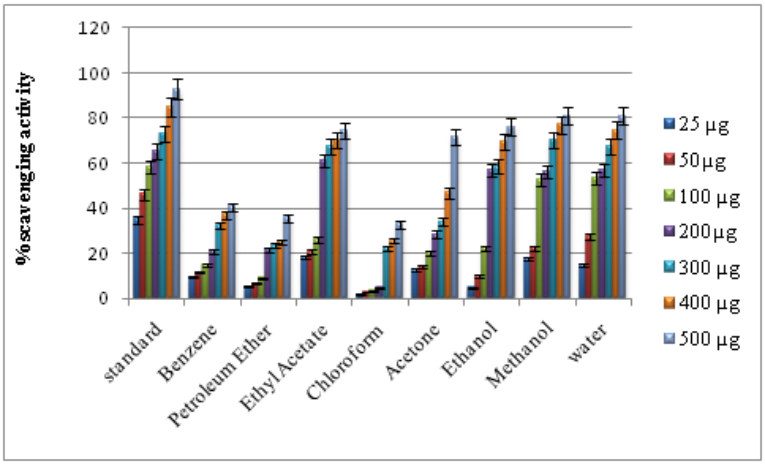
Nitric oxide radical scavenging assay

The assay was carried out as reported by Shirwaikar and Somashekar[13] and Sreejayan and Rao[14].

Results and Discussion

DPPH radical scavenging activity

DPPH is a nitrogen centered free radical which can exert absorbance at 520 nm. It can be easily scavenged by antioxidants or free radical scavengers[15]. It is mainly employed to analyze the free radical scavenging ability of food samples and plant samples[16, 17]. Figure 1 indicates the antioxidant activities of various solvent extracts of *Tabebuia pallida* using ascorbic acid as the standard. Among the various samples tested the intense scavenging



Values are represented in ±SD for triplicates in each category

Figure 1
DPPH radical scavenging activity of *T.pallida*

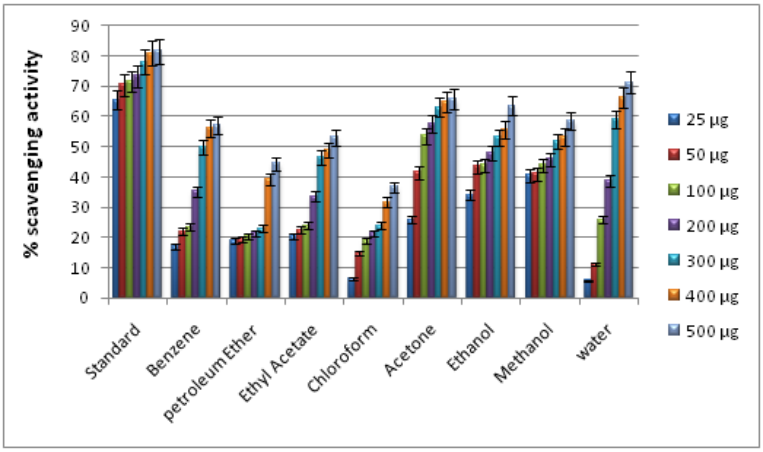
potential was observed in methanol, ethanol and aqueous extracts. The potential was observed to be increased when the sample concentration increases. It is evident from Figure 1 that the other extracts tested were also found to possess the significant scavenging potential.

DPPH radical scavenging ability of various extracts of Tabeubia pallida leaves

In line with our study Rajani *et al*[18] tested the ability of 6 different leafy vegetables to scavenge the DPPH radical. The findings of their study declared that the highly polar solvent extracts like ethanol and methanol acts as potent DPPH radical scavengers when compared to non polar solvent extracts like hexane.

ABTS radical scavenging activity

ABTS radical scavenging activity is the classic method for the study of antioxidant effects of plant extracts. The effectiveness of the extracts and the standard was determined by the degree of discoloration of the ABTS mono cation which is measured spectrophotometrically at 745 nm[19]. The data indicate that the varying concentrations of the extracts manifested different level of scavenging potential for ABTS radicals in dose proportional manner. Among the tested extracts the acetone, ethanol, methanol and water extracts were able to quench the ABTS mono cation even at their lower concentration (Figure 2). Acetone exerts 25.85% scavenging ability still at a concentration of 25 µg/ml, and also the ethanolic and methanolic extracts



Values are represented in ±SD for triplicates in each category

Figure 2
ABTS radical scavenging activity of *T.pallida*

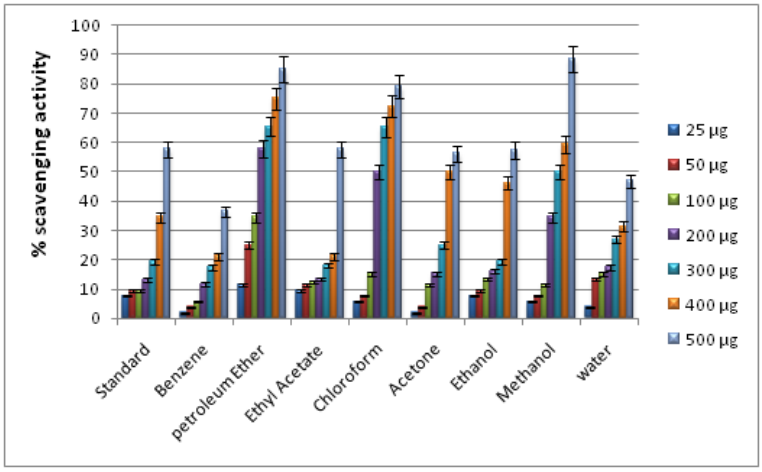
scavenge 34.14 and 40.48% respectively. The scavenging potential is observed to be increased when the concentration of the sample increases.

ABTS radical scavenging ability of different solvent extracts of Tabeubia pallida

In yet another report by Lalhminghlui and Ganesh[20], various extracts of (ethanol, chloroform and water) *S. wallichii* manifested a hike in the scavenging of ABTS radicals in a dose proportional manner. Among all the three extracts tested ethanol extract is found to be the best ABTS radical scavenger even in its lower concentration.

Hydroxyl radical scavenging activity

Hydroxyl radical is an oxygen centered species which is highly labile and causes extreme destruction to the cells when compared to the other Reactive Oxygen Species[21]. Since it causes severe damage to the cells, the elevation of these radicals lead to several complications including cancer, ageing and several other disease conditions[22]. As shown in Figure 3, of the several extracts tested chloroform, petroleum ether, and methanolic extract of *T.pallida* were able to hunt the hydroxyl radical in a dose proportional manner. It is noticed that these three solvent extracts can able to hunt the $^{\bullet}OH$ much more effectively than the reference standard ascorbic acid. All the other extracts and standard ascorbic acid showed a significant scavenging potential against hydroxyl radicals.



Values are represented in ±SD for triplicates in each category

Figure 3
Hydroxy radical scavenging activity of *T.pallida*

Hydroxyl radical scavenging activity of different solvent extracts of Tabeubia pallida

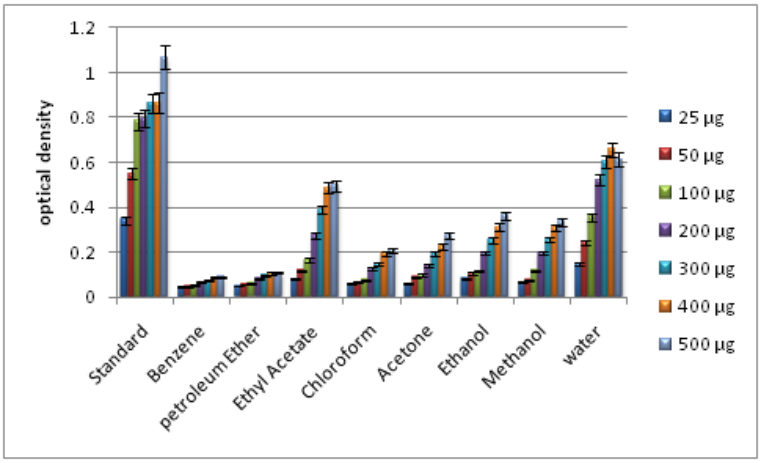
Irshad *et al*[23] studied the hydroxyl radical hunting ability of seed and pulp extracts of *Cassia fistula*. The study suggests that the methanolic extract of the seeds and pulp scavenge the hydroxyl radicals in a dose proportional manner. The efficacy was found to be more for the pulp than the seeds.

Reducing power assay

Reducing power of the various solvent extracts of *T. pallida*, was analysed and the findings are indicated in Figure 4. The aqueous extract manifested the elevated reducing potential, whereas the ethyl acetate extract manifested almost equal efficacy. All the solvent extracts exhibited more or less related increasing trend in reducing power when the concentration increases.

Reducing power assay of various solvent extracts of Tabeubia pallida leaves

Irshad *et al*[23] conducted a study on reducing potential of various extracts of *Cassia fistula* using ascorbic acid as the standard. Among the various extracts tested methanol solvent extracts of pulp and seed showed high activity. Jayanthi and Lalitha[24] studied the reducing potential of ethyl acetate, acetone, petroleum ether, and water extracts of *Eichhornia crassipes* (Mart.) Solms and observed that the reducing ability of all the extracts elevated when concentration of the extracts increases.



The values are represented in ±SD for triplicates in each category

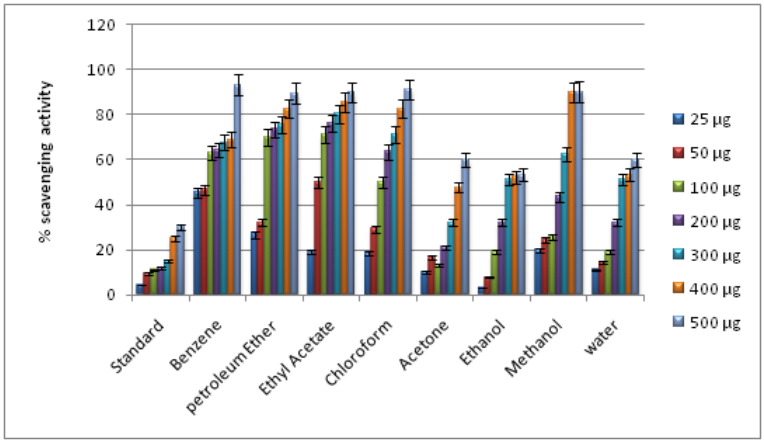
Figure 4
Reducing power assay of *T.pallida*

Nitric oxide radical scavenging activity

Macrophages, neurons and endothelial cells generate an important chemical mediator, nitric oxide which plays a crucial function in the regulation of normal physiological processes when it is in optimum concentration[25]. When the concentration exceeds its optimal level it is usually associated with several diseases[26]. So plant extracts can be used to scavenge the excess nitric oxide radical that causes various ailments. In the present study, the various extracts of *T.pallida* have been screened against nitric oxide radicals and it was observed that the scavenging effect of various solvent extracts is in the subsequent sequence: benzene > chloroform > methanol > ethyl acetate > petroleum ether > water > acetone > ethanol. The free radical hunting ability of the ascorbic acid standard was found to be very less when compared to the various extracts.

Nitric oxide radical scavenging ability of various extracts of Tabebuia pallida leaves

In line with the current study, Rozina *et al*[27] screened the three healing plants namely *Casuarina littorea*, *Phyllunthus freternus* and *Triumfetta rhomboidae* (methanolic extracts) for their nitric oxide radical hunting potential. All the solvent extracts tested were able to produce significant NO scavenging potential in a dose proportional fashion. Among the various solvent extracts tested, *Phyllunthus freternus* proved high scavenging activity and roots of *Triumfetta rhomboidae* exerted least scavenging potential.



Values are represented in ±SD for triplicates in each category

Figure 5
Nitric oxide radical scavenging activity of *T.pallida*

Conclusion

The various solvent extracts of *Tabebuia pallida* were observed to exhibit antioxidant properties in a dose proportional fashion. DPPH radicals were effectively scavenged by methanol and aqueous extracts. Acetone extract of *Tabebuia pallida* is effective against ABTS radical even in its lowest concentration and also ethanol, methanol and aqueous extract showed a better scavenging action. Petroleum ether, chloroform and methanolic extract of *Tabebuia pallida* is very much more effective against hydroxyl radical than the reference compound Ascorbic acid. Ethyl acetate and water extract showed an equal potential in reducing power assay. Non polar solvent extracts like benzene, chloroform, petroleum ether and ethyl acetate are much effective against nitric oxide radicals. From the above study, it is evident that the plant based antioxidants are much effective against the free radicals. The major advantage of these antioxidants from plant origin is that they produce very less or no side effects. So the antioxidants from these medicinal plants can be purified and used for therapeutic purposes rather than synthetic antioxidants which lead to adverse side effects.

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Conflict of Interest

All authors declare that they do not have conflicts of interest.

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4.	Name of the Research Guide	Dr. R. Nirmaladevi
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