RESEARCH PAPER

Antioxidant, Anti-Inflammatory And Neuroprotective Properties Of *Bruguiera Sexangula* (Lour) Poir And *Avicennia Officinalis* L. Blume

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Abstract

Neurodegenerative diseases have become the greatest challenge in the modern world due to the increase in life expectancy and the lack of effective treatments. In this context, bioactive compounds like phenols and flavonoids can play a major role due to their pharmacological potential. The current study investigated the preliminary phytochemical screening, antioxidant, anti-inflammatory and neuroprotective activities of *Bruguiera sexangula* (BSL) and *Avicennia officinalis* leaves (AOL) methanolic extracts. DPPH and ABTS scavenging assays were employed to determine the antioxidant activity, and the egg albumin denaturation assay to assess the anti-inflammatory property. Further neuroprotective efficiency was evaluated on H_2O_2-exposed SH-SY5Y cells. The phytochemical screening revealed the presence of different bioactive compounds in both the extracts. However, BSL extract exhibited comparatively higher antioxidant and anti-inflammatory activities than AOL due to its higher phenol and flavonoid content. The pretreatment of BSL and AOL significantly mitigated H_2O_2-induced oxidative damage in SH-SY5Y cells by improving the cell viability and reducing the ROS generation. This study highlights the promising antioxidant, anti-inflammatory and neuroprotective role of BSL and AOL. However, further detailed in vitro investigations are needed to validate their mechanism of action.

Keywords- Antioxidant, anti-inflammatory, neuroprotective, SH-SY5Y cells, ROS, mangrove, H2O2.

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Introduction

Neurodegenerative diseases (ND) are malfunctions of the nervous system that affect the elderly population worldwide[1]. ND is characterized by the gradual deterioration of neuronal structure and function in specific regions of the brain, and includes Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, and Huntington's disease[2]. ND are known to share a common mechanism, which includes mitochondrial dysfunction, aggregation of proteins, inflammation, and oxidative stress[3]. Specifically, oxidative stress (OS) plays a foremost role in the development of these diseases[4,5].

OS results from uncontrolled radical generation, such as reactive oxygen and nitrogen species, that damages cellular biomolecules[6,7]. Therefore, understanding the effect of the OS on the progression of ND is crucial for improving therapeutic strategies. Excessive OS also initiates an inflammatory reaction, thus making OS and inflammation key factors in ND[8]. Presently, commercially available drugs for ND offer short-term symptomatic relief with long-term side effects[9]. Thus, there is a critical need for a new, safe, effective alternative for the management of ND.

Recently, natural antioxidants have become the centre of attraction due to their free radical-quenching properties[10,11]. Therefore, plants and their products have been studied widely, highlighting their effectiveness in the treatment of ND[12,13,14,15]. Mangrove plants are halophytes that grow in tropical and subtropical coasts[16]. They thrive in extreme conditions and produce distinct phytocompounds with biological properties[17,18]. Several species of mangrove have been traditionally used to treat various conditions, which has gained the attention of researchers.

Bruguiera sexangula (Lour.) Poir is a true mangrove, belonging to the Rhizophoraceae family. It is commonly known as the orange mangrove and is distributed in the Indo-West Pacific region[19]. It can grow up to 30 m tall with grey-coloured bark, and its leaves are simple and opposite[20]. The leaves and bark have remedial properties, like antidiabetic, antioxidant, and anticancer activities[21, 22].

Avicennia officinalis L. is another true evergreen mangrove. It belongs to the Acanthaceae family, also referred to as white mangrove, and is widely distributed along the coast of India[23, 24]. The different pharmacological investigations reported the

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antimicrobial, antioxidant, antidiabetic, anticancer, antiulcer, and anti-inflammatory activities of this plant[25,26,27,28]. Its seeds and bark have been used to treat smallpox sores, abscesses, boils, scabies, etc.[29] However, no studies have been reported on the neurological effects.

Therefore, the present study was carried out to evaluate the antioxidant and anti-inflammatory activities of *Bruguiera sexangula* and *Avicennia officinalis* leaf extract and their neuroprotective role on H_2O_2-induced oxidative stress in SH-SY5Y cells.

Materials and Method

Chemicals and reagents

2, 2 - Di (4-tert-octyl phenyl)-1-Picryl Hydrazyl (DPPH), 2, 2 -Azinobis -3-ethylbenzothiazoline-6-sulphonic acid (ABTS), Dichloro difluorescein diacetate (DCFDA), Thiobarbituric acid, Streptomycin, penicillin, Dulbecco's Modified Eagle Medium/F12 (DMEM/F12), trypsin-EDTA, antibiotic and antimycotic solution, phosphate-buffered saline (PBS) and Fetal bovine serum (FBS), 3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide (MTT), were procured from Himedia. H_2O_2, Dimethyl sulfoxide (DMSO), and other chemicals were from SRL.

Collection of plant material

Fresh leaves of *Bruguiera sexangula* (Lour) (BSL) and *Avicennia officinalis* L. Blume (AOL) were collected from Udupi region from Karnataka and Dr. V. Rama Rao, CARI, Bengaluru, Karnataka, identified the samples (RRCBI mus-363 and 364, respectively).

Preparation of extract

The methanolic extract of the leaf of *Bruguiera sexangula* (Lour) and *Avicennia officinalis* L. Blume by following the procedure of Suganthy and Devi[30]. Briefly, the collected fresh leaves were washed, dried, and finely ground with a blender. 10 gm of fine powder was dissolved in 100 mL of methanol, stirred for 24 h at room temperature, filtered, evaporated and kept at 4 °C. The percentage of yield was determined by using the given formula.

$$\% \text{ Yield} = \frac{W1}{W2} \times 100$$

Where, W1 and W2- weight of the dried extract and plant powder.

Phytochemical analysis

The various phytochemical constituents, such as saponins, glycosides, phenols, tannins, alkaloids, carbohydrates, terpenoids, flavonoids, and steroids, were analysed by standard methods of Yadav et al.[31] and Bankole et al.[32]

Ultraviolet- visible spectral analysis

The BSL and AOL extracts were subjected to UV-visible spectral analysis[33]. The absorbance spectra of the extracts were recorded after diluting them to 10 times using methanol (extraction solvent) at 200 to 800 nm (UV-VIS spectrophotometer)

Measurement of total phenolic (TPC) and flavonoid content (TFC)

The Siddiqui et al.[34] procedure was used to measure the TPC of BSL and AOL extracts. Briefly, extract (1mL) and 7.5% sodium carbonate (4 mL) were added with Folin-Ciocalteu reagent and subjected for incubation (30 min). The absorbance was taken at 765 nm and expressed as gallic acid equivalents (mg/g).

To assess the TFC of BSL and AOL extracts the protocol of Meda et al.[35] was employed. Briefly, aluminium trichloride (2%) and extract were mixed in equal proportion and read at 415 nm after 10 min of incubation. The results were represented as mg of quercetin equivalents (mg/g).

Measurement of Antioxidant Activities

DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay

The DPPH activity of extracts was determined by method of Shon et al.[36] Briefly, 0.04% DPPH and extract were combined and incubated (20 min) and recorded at 517 nm.

ABTS (2, 2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)) radical assay

The Lee et al.[37] methodology was followed to measure the ABTS activity of the extract. Briefly, $ABTS^+$ were prepared from ABTS (7mM) and potassium persulfate (2.4 mM) (1:1) and incubated for 12 h in the dark. After adjusting the absorbance at 0.700, 900µL of the solution and 100 µL extract were mixed and at 734 nm, the absorbance was taken.

The given equation was used to calculate the scavenging activity for the DPPH and the ABTS assays.

$$\text{Scavenging (\%)} = \frac{(\text{Abs control} - \text{Abs sample})}{\text{Abs control}} \times 100$$

In vitro anti-inflammatory activity

The anti-inflammatory activity of the BSL, AOL and standard Diclofenac sodium was measured[38]. Briefly, 0.2 ml egg albumin was incubated for 15 min with 2.8 ml PBS (pH 6.4) and 2 ml of extract. The mixture was heated (70 ºC for 5 min), cooled, and recorded at 660 nm. The percentage inhibition was obtained using the following formula:

$$\% \text{ Inhibition} = \frac{(\text{Abs control} - \text{Abs sample})}{\text{Abs control}} \times 100$$

In vitro studies

Cell culture and maintenance

The SH-SY5Y cells were obtained from the NCCS (National Centre for Cell Sciences) Pune and cultured in medium enriched with DMEM and Ham's F-12, 10% FBS, L-glutamine, and 1% penicillin and streptomycin in 5% CO_2-humidified incubator at 37 ºC. The medium

was regularly replaced and the cells were sub-cultured after reaching the 75-80% confluency using trypsin.

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay

The cytotoxicity of BSL and AOL extracts was assessed using MTT on the SH-SY5Y cells following the protocol of Mosmann[39]. The cells were plated at a 10×10^3 cells/well density (96-well plate) and treated with extracts at different doses for 24 h, further incubated at 37°C with MTT (5mg/mL) for 4 h. Then, DMSO (100µL) was added, and read at 570 nm. (Synergy LX, Agilent Technologies). The doses with more than 80% viability were selected to assessed the neuroprotective effect against H_2O_2-exposed SH-SY5Y. The cells were pretreated (2 h) with BSL and AOL before the H_2O_2-exposure for 24 h, followed by MTT assay as explained above.

Neutral red uptake assay (NRU)

The NR assay was performed by following Repetto et al.[40] staining protocol. Briefly, the SH-SY5Y cells were seeded (96-well plate at a 10×10^3 cells/well), and pre-treated as explained above. The cells were further incubated with 40 µg/mL NR (2 h, 37 °C), then destained with 50% ethanol and 1% glacial acetic acid and read at 540 nm (Synergy LX, Agilent Technologies).

Measurement of intracellular ROS

The ROS formation was quantified using methodology of Periyakaruppan et al.[41] Briefly, the cells were seeded and pretreated with extracts and or with H_2O_2 as mentioned above then washed with PBS and incubated with DCF-DA (100 µL) at 37 °C (30 min). The fluorescence was recorded using Synergy LX (Agilent Technologies) at an excitation: 488 nm and emission: 525 nm.

Statistical analysis

All the data were acquired in triplicate and expressed as mean ± SE. The data was then analysed by one-way and two-way analysis of variance (ANOVA) followed by Tukey's test.

Results

Extraction yield and preliminary phytochemical analysis

The percentage yield of BSL and AOL was 19.83 and 17.52, respectively. The screening of phytoconstituents in BSL and AOL showed the presence of Flavonoids, phenolics, tannins, saponins, and carbohydrates. However, alkaloids were present in BSL, and glycosides and terpenoids were present in AOL extract (Table 1)

Table 1. Phytochemical constituents in the methanolic extracts of *Bruguiera sexangula* and *Avicennia officinalis* leaves

Phytoconstituents	*Bruguiera sexangula*	*Avicennia officinalis*
Phenols	+	+
Tannin (Braymer's test)	+	+
Saponin (Foam test)	+	+
Flavonoids	+	+
Glycosides (Liebermann's Test)	-	+
Steroids (Salkowski test)	-	-
Carbohydrates (Molisch's Test)	+	+
Alkaloids (Hager's Test)	+	-
Terpenoids	-	+

+ indicates presence, -indicates absence

UV-visible spectral analysis of the extracts

The UV-visible spectrum analysis of BSL and AOL extracts revealed the maximum absorptions at 356 nm, 475nm, 663 nm, and 273 nm, 412 nm, 665nm, respectively, as shown in Fig. 1.

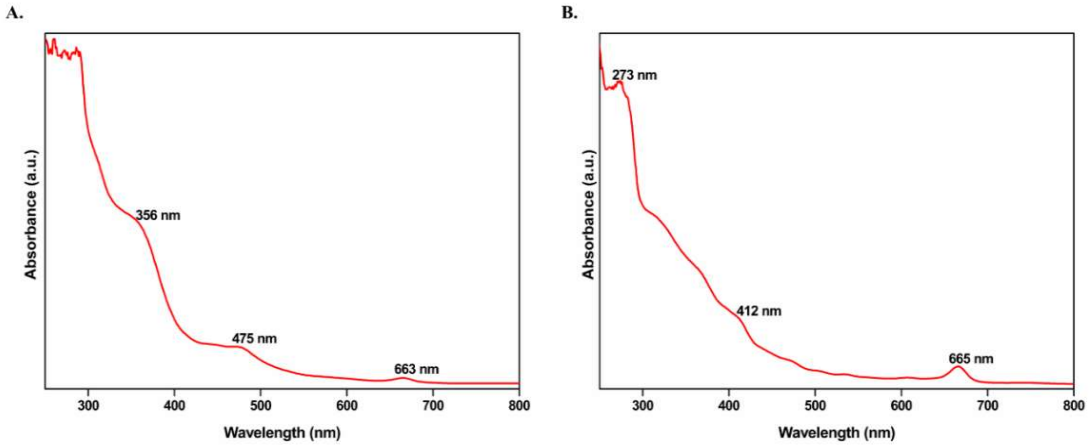

Fig. 1. Ultraviolet – visible spectrum of the methanolic extract of A) *Bruguiera sexangula* leaves and B) *Avicennia officinalis* leaves.

Total phenol and flavonoid estimation

The total phenol and flavonoid contents of the extracts are represented in Table 2. The significant difference was observed in both the extract with the highest value of total phenol (199±2.71 mg GAE/g) and flavonoid (106±0.10mg Qu/g) was found in the BSL extract as compared to the AOL extract (88±15.69mg GAE/g and 75±0.37mg Qu/g), respectively.

Table 2. The total phenolic content in the methanolic extracts of *Bruguiera sexangula* and *Avicennia officinalis* leaves

Plants	Total phenolics mg GAE/g	Total flavonoids mg Quercetin/g
Bruguiera sexangula	199±2.71[a]	106±0.10[c]
Avicennia officinalis	88±15.69[b]	75±0.37[d]

The values were represented as mean ± SE (n=3) and analyzed through two-way ANOVA followed by Tukey's test. Different superscript letters indicate significant differences between the samples (p <0.05).

Antioxidant assay

The dose-dependent DPPH and ABTS radical-scavenging activity was noted in all the extracts (Fig. 2). The IC_{50} value for DPPH activity of BSL was determined as 6±0.11µg/mL, and that of AOL is 21± 4.26 µg/mL. Similarly, ABTS assays also revealed higher activity in BSL (43±0.13 µg/mL) than AOL (60±1.80 µg/mL) (Table 3).

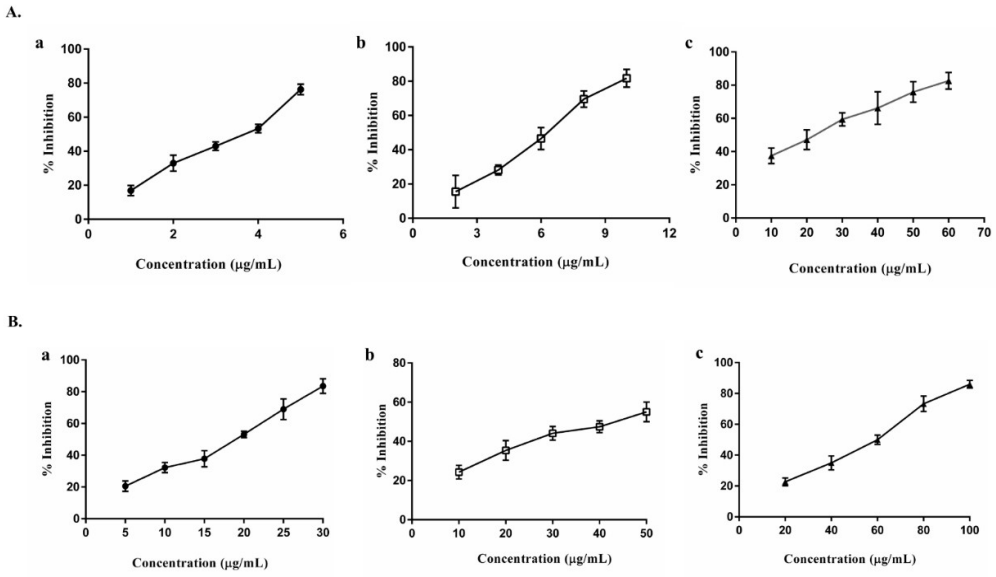

Fig. 2. A) DPPH radical scavenging activity of a) ascorbic acid, b) *Bruguiera sexangula* leaves extract and c) *Avicennia officinalis* leaves extract, B) ABTS radical scavenging activity of a) ascorbic acid, b) *Bruguiera sexangula* leaves extract, and c) *Avicennia officinalis* leaves extract. The values were represented as mean ± SE (n=3).

In vitro anti-inflammatory assay

In an in vitro anti-inflammatory assay, the BSL and AOL extracts exhibited dose-dependent inhibition with an IC_{50} value of 2091±0.40 and 2703±0.19 µg/mL, respectively, as shown in Table 3.

Table 3. The IC_{50} values for DPPH, ABTS, and *in vitro* anti-inflammatory in the methanolic extracts of *Bruguiera sexangula* and *Avicennia officinalis* leaves

Samples	DPPH (µg/mL)	ABTS(µg/mL)	Anti-inflammatory activity (µg/mL)
Bruguiera sexangula	6±0.11[a]	43±0.13[c]	2091±0.40[e]
Avicennia officinalis	21± 4.26[b]	60±1.80[d]	2703±0.19[f]
Ascorbic acid	4±2.40[a]	19±1.23[b]	-
Diclofenac sodium	-	-	617±0.20[g]

The values were represented as mean ± SE (n=3) and analyzed through two-way ANOVA followed by Tukey's test. Different superscript letters indicate significant differences between the samples (p <0.05).

***In vitro* studies**

Cytotoxic effect of BSL and AOL on SH-SY5Y cells

The cytotoxic activity of BSL and AOL on SH-SY5Y cells was determined by MTT assay. The cells were treated with BSL and AOL at doses (12.5 to 200 µg/mL) for 24 h. As elucidated in Fig. 3, BSL and AOL-treated cells showed non-toxicity below the concentration 100 µg/mL. Hence, these concentrations used to demonstrate the neuroprotective effect of both the extracts on H_2O_2-induced oxidative stress in SH-SY5Y cells. The IC_{50} of 135 µM H_2O_2 was selected based on our previous investigation[42].

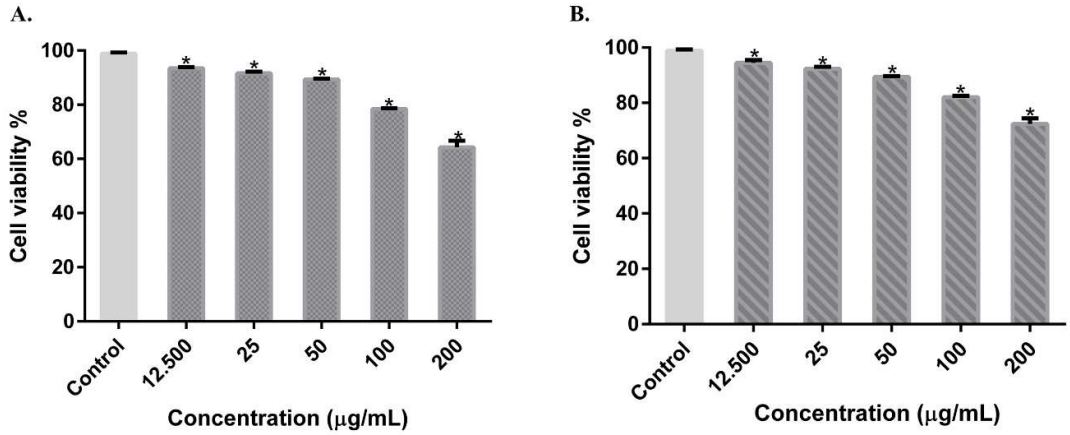

Fig. 3. Effect of A) *Bruguiera sexangula* and B) *Avicennia officinalis* leaves extract on SH-SY5Y cells. The data are expressed as mean ± SE (n=3) and analysed by one-way ANOVA followed by Tukey's test. * Indicates p <0.05 significance compared to the control.

Neuroprotective effect of BSL and AOL

The neuroprotective effects of BSL and AOL extracts were examined on H_2O_2-induced SH-SY5Y cells by pre-treating with non-toxic concentrations for 2 h, followed by H_2O_2 (24 h). The concentrations of 25 and 50 µg/mL showed up to 60 to 80% of increase in cell viability. The obtained results can be further corroborated by microscopic examination. As shown in Fig. 4, morphological alterations, such as the shrinkage of the cell and neurites, can be observed in H_2O_2-treated cells, comparable to control and recovery from oxidative stress can be seen in the pretreated cells (50 µg/mL) compared to H_2O_2 alone.

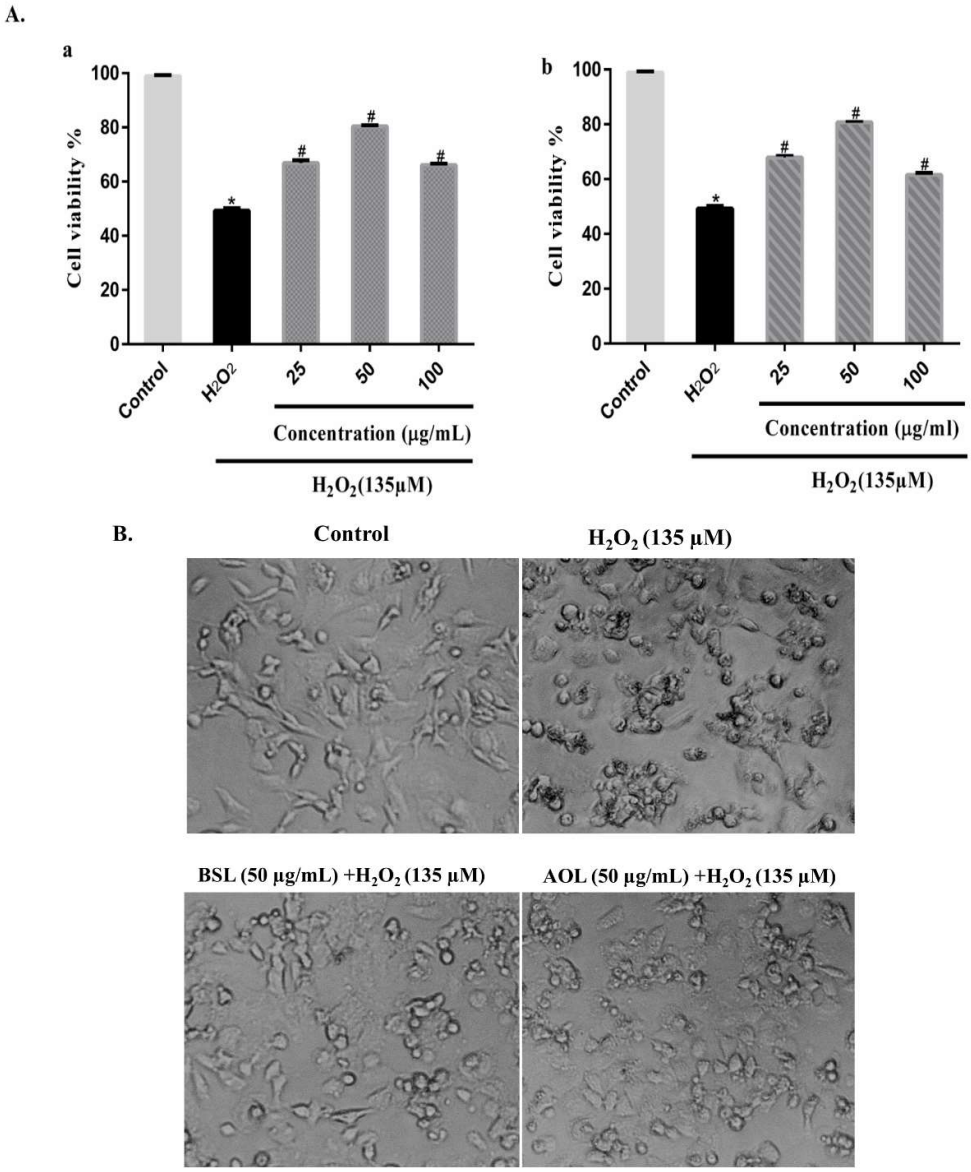

Fig. 4. Neuroprotective effect of A) a) *Bruguiera sexangula* and b) *Avicennia officinalis* leaves extract on H_2O_2-induced cytotoxicity in SH-SY5Y cells. B) Morphological images of H_2O_2-induced SH-SY5Y cells. The data are expressed as mean ± SE (n=3) and analysed by one-way ANOVA followed by Tukey's test. *Indicates p <0.05 significance compared to the control. # indicates p <0.05 significance compared to the H_2O_2. (magnification-20X).

Neutral red uptake assay (NRU)

To validate the MTT assay, the NRU assay was executed in pre-treated H_2O_2-induced SH-SY5Y cells to determine the cell viability. Fig 5 demonstrated that the treatment with 135 µM H_2O_2 alone has substantially decreased the cell viability by 53% compared to control cells. On the contrary, a significant increase in viability was obtained in BSL (50 µg/mL) and AOL (50 µg/mL) extracts pre-treated cells compared to H_2O_2 alone at 79% and 75% concentrations, respectively.

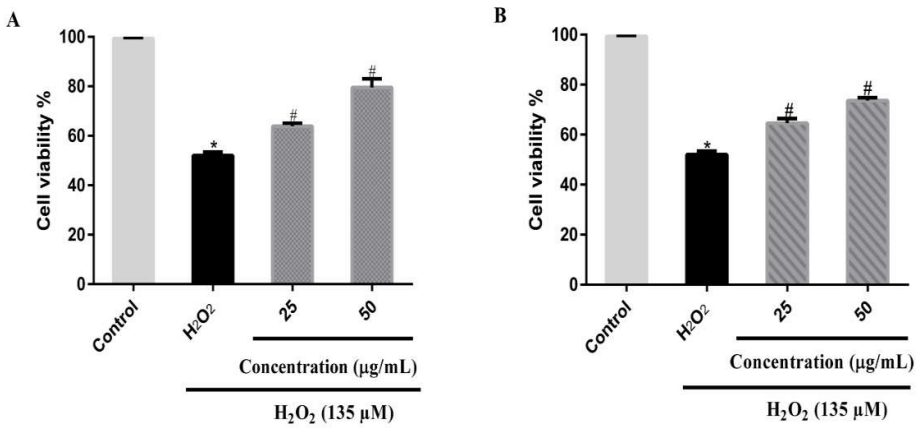

Fig. 5. Effect of A) *Bruguiera sexangula* and B) *Avicennia officinalis* leaves extract on H_2O_2-induced cytotoxicity in SH-SY5Y cells by neutral red uptake assay. The data are expressed as mean ± SE (n=3) and analysed by one-way ANOVA followed by Tukey's test. *Indicates p <0.05 significance compared to the control. # indicates p <0.05 significance compared to the H_2O_2.

ROS scavenging assay

The H_2O_2 exposure has significantly elevated the ROS generation by 82% compared to the control. The pre-treatment with BSL and AOL at 25 µg/mL and 50 µg/mL has dose-dependently lowered the ROS levels up to 13% and 35%, respectively, comparable to H_2O_2 (Fig. 6).

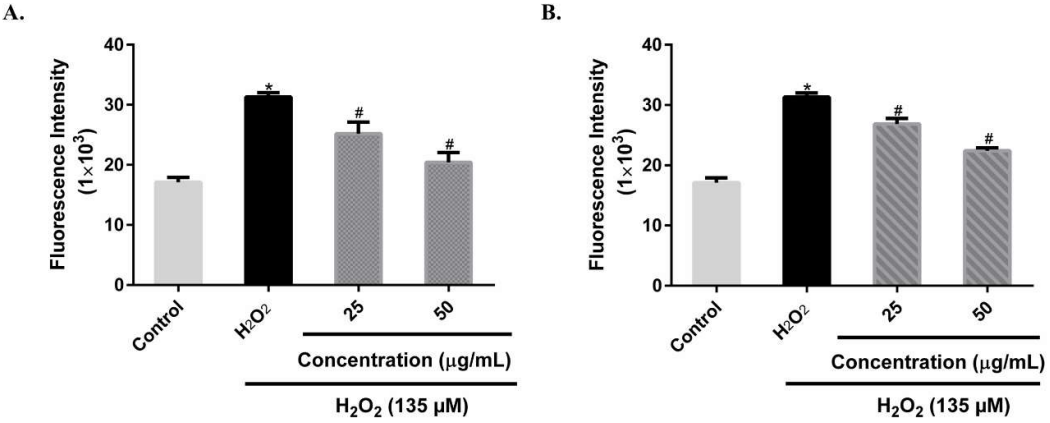

Fig. 6. Effect of A) *Bruguiera sexangula* and B) *Avicennia officinalis* leaves extract on reactive oxygen species (ROS) generation in H_2O_2-induced cytotoxicity in SH-SY5Y cells. The data are expressed as mean ± SE (n=3) and analysed by one-way ANOVA followed by Tukey's test. *Indicates p <0.05 significance compared to the control. # indicates p <0.05 significance compared to the H_2O_2.

Discussion

Neurodegenerative diseases are resultant of gradual damage of neurons in a specific region of the brain[43]. The brain has a high demand for oxygen and relatively lower antioxidant enzyme levels, which make it more vulnerable to OS[44]. OS has a fundamental role in the ND's development by inducing neuronal apoptosis and inflammation[45]. Recently, plant-derived biomolecules like polyphenols, terpenoids, and alkaloids have been studied in depth due to their anti-inflammatory, antioxidant, and cytoprotective activities. Therefore, the current study investigated the antioxidant, anti-inflammatory and neuroprotective potential of BSL and AOL extracts.

Bruguiera sexangula (BS) and *Avicennia officinalis* (AO) are known to possess different secondary metabolites[46,22]. In accordance, our results also exhibited the presence of various phytocompounds like phenols and flavonoids[47]. They support plants' antioxidant capacity by scavenging free radicals, chelating metals, and donating electrons[13]. The total phenol and flavonoid contents of the BSL extract were higher than those of the AOL extract. Similar results were observed in the UV-VIS spectrum, with BSL showing a band around 360 nm that indicates the presence of a flavonoid[48]. Whereas the AOL extract contains terpenoids and glycosides. BSL also showed higher DPPH and ABTS activities than AOL extract due to higher phenols and flavonoid

content. Our results are in accordance with earlier studies that reported the antioxidant activity in different parts of BS and AO extract[28,23,49]. The difference in antioxidant activity between the extracts may be due to variability in their bioactive content[50]. Similarly, the BSL extract exhibited greater anti-inflammatory activity by inhibiting heat-induced egg albumin denaturation, which could be attributed to its higher flavonoid content[51]. Our results are in concord with previous studies, which showed phytocompounds from plant extracts exhibit anti-inflammatory activities[52,53].

The neuroprotective activity of BSL and AOL was evaluated on H_2O_2-induced SH-SY5Y cells using MTT and NRU assay, which is a widely used in vitro model to induce OS[54,55,56]. Our results revealed the dose-dependent cytoprotective activity of both the extracts. Further NRU assay confirmed the neuroprotective effect, in which viable cells take up neutral red in their lysosomes[57]. Further, morphological examination revealed that the pretreatment of extracts attenuated the H_2O_2-induced morphological alterations by improving cellular integrity and modulating oxidative stress due to bioactive compounds like phenols and flavonoids present in extracts. Similarly, the presence of terpenoids in AOL extracts supports its protective ability[58].

The H_2O_2 is highly membrane permeable; it enters rapidly and generates extremely reactive OH radicals that damage cellular components, in turn generating more ROS[59]. The ROS can be assessed by DCF-DA assay, where 2′,7′-dichlorodihydrofluorescein (DCFH) undergoes oxidation and forms fluorescent DCF (Dichlorofluorescein)[60]. H_2O_2-alone-treated cells showed increased levels of ROS, whereas the extract-pretreated group showed reduced levels of ROS, suggesting that extracts significantly.

Conclusion

The current study revealed that phenol- and flavonoid-rich extracts of *Bruguiera sexangula* and *Avicennia officinalis* leaves exert antioxidant and anti-inflammatory activities, as indicated by lower IC_{50} values. Further, the extracts demonstrated their neuroprotective role against H_2O_2-induced damage in SH-SY5Y cells by mitigating oxidative stress and reducing intracellular ROS production. These findings suggest that *Bruguiera sexangula* and *Avicennia officinalis* leaf extracts may be considered as a neuroprotective agent, but further detailed *in vitro* and *in vivo* studies are required to validate their therapeutic potential.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding this paper.

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