Research Paper

Enhancing Synthesis of Mycosporine-Like Amino Acids from Cyanobacteria: Characterization, Analysis and *In Vitro* Anticancer Study

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Mycosporine like amino acids are small extra-cellular metabolites, which are produced by diverse group of microorganisms including cyanobacteria; possess photo protectant and antioxidant action. The goals of this work include increasing the productivity of Mycosporine like amino acids in cyanobacteria, identification and description of these metabolites using Fourier transform infrared and high-performance liquid chromatography, and evaluation of the cytotoxic activity of the investigated cyanobacterial extracts *in vitro*. The outcomes extend the current knowledge of Mycosporine like amino acids biomedical utility and lay the foundation for the development of their therapeutic potential.

Key words: Mycosporine, amino acids, cyanobacteria, photo protectant, antioxidant action

The impact of Ultraviolet (UV) radiation from the sun is destructive to nucleic acids, proteins, and lipids of all living organism. Even though, the detrimental effects of UV radiation cannot be avoided by simply covering the skin, many organisms possess UV-absorbing compounds like the Mycosporine-Like Amino Acids (MAAs)[1]. MAAs are small, water soluble compounds incorporating a cyclohexanone or cyclohexenimine chromophore directly conjugated to a side chain derived from an amino acid or an amino alcohol. They show high absorption in the UV region of the spectrum ranging from 310-365 nm, and act as natural sunblock, shielding the cells against UV deficient damage[2]. Of all the sources of MAAs, cyanobacteria deserve special attention.

Cyanobacteria are photosynthetic microorganisms found in various extreme conditions and are thus the most efficient producers of bioactive substances, such as MAAs[3,4]. These organisms have been the focus of many researchers interested in understanding the nature of MAAs synthesis under different stress factors such as UV radiation, high salinity, and low nutrient concentrations[5]. Other practical uses arising from the biotechnological prospect of cyanobacteria include its ease of genetic modification and their fast growth dynamics. MAAs have received much attention because they are involved in many functions besides UV protection[6]. It shows antioxidant; anti-inflammatory and anti-aging properties thus making them useful in the production of cosmeceutical products.

The latter has recently also been demonstrated to possess anticancer properties in several investigations[7]. MAAs can suppress cancer cell growth and stimulate cell death through regulating levels of oxidative stress and signalling pathways[8]. These properties can entitle MAAs as potential candidates for designing new untainted anticancer agents[9]. While and their biotechnological applications have been identified in cyanobacteria, the cellular quantities of MAAs often do not meet the requirements for commercial production[10]. Metabolic engineering approaches, improvement of the cultivation conditions, and studying stress-inductive conditions are the major directions for further research[11]. Pharmacogenomics work has revealed enzymes implicated in MAA synthesis including dehydroquinate synthase and

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O-methyltransferase, which can be genetically adjusted to increase MAA yield.

Identifying the structure and properties of MAAs is therefore crucial towards the elucidation of the biosynthetic routes and the activity profiles. Currently, High-Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), and Nuclear Magnetic Resonance (NMR), are most frequently used for MAA identification and quantity measurement. Advanced techniques in the analysis have allowed the identification of numerous MAAs with peculiar UV-VIS absorption and biological activities[6].

To date, there seem to be little understanding of the ability of MAAs to possess anticancer activity[2]. Several authors have stated that some MAAs selectively exhibit cytotoxic behaviours towards cancer cells and are harmless toward healthy cells[12]. At the molecular level, MAAs help to control Reactive Oxygen Species (ROS) and, consequently, oxidative stress mediated Deoxyribonucleic Acid (DNA) damage and apoptosis in cancer cells. In cancer cells the same oxidative stress modulation may affect the redox balance and result in cell death[13]. Moreover, MAAs have also been found to regulate important molecular pathways such as Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) and Mitogen-Activated Protein Kinase (MAPK), which are dysregulated in cancer cells[14].

The focus of the commenced study is to improve the MAA biosynthesis in cyanobacteria through environmental manipulation, to characterize the isolated MAA's physicochemical properties and to evaluate their in-vitro anticancer properties. The present study could therefore set the tone for the institutionalization of MAAs as affordable and realistic biomolecules in the pharma and cosmetic industries.

MATERIALS AND METHODS

Collection of cyanobacteria:

The cyanobacterial species used in the current study were *Oscillatoria* species (BDU 14219) obtained from the National Facility for Marine Cyanobacteria (NFMC), Bharathidasan University.

Cultivation of cyanobacteria[15]:

Oscillatoria species were isolated under laboratory culture experiments. Preliminary studies on the physiology of MAA synthesis involving light intensity (50 µ mol-2 s^{-1}), temperature (25°), and nutrient composition (modified BG-11) were used. Samples were harvested in the exponential phase of growth, when the cells were producing large quantities of metabolites on which the cultures were fed.

Extraction and purification of MAAs:

The extraction of MAAs was done using the procedure described[16]. Firstly, cyanobacterial crust was washed three times with Millipore water to wash off dust particles and other contaminants. The cleaned crust was lyophilized and the dried mat was then mechanically homogenized to powder with a micro pestle.

The latter was followed by the suspension of 1 g of the powdered biofilm in 20 ml of 100 % HPLC grade methanol at 4° for 12 h. The sample was sonicated for 1 min and centrifuged at 10 000×g for 5 min. The supernatant was left to dry at room temperature[17].

Finally, ultra-pure water was use to dissolve 650 µl of the dried extract; the solution was again subjected to the centrifuge at 10 000×g for 5 min to filter away water insoluble substances. 100 µl of chloroform was added to the solution and the solution was mixed using a vortex. The purified MAAs float in the upper aqueous layer, while the lipophilic pigments and other contaminants are in the lower organic phase, thus, the upper aqueous layer was carefully transferred to the Eppendorf tubes.

Last, the purified extract was filtered using a 0.22 µm micro centrifuge type syringe filter to produce the sample prior to its use in HPLC.

UV-Vis spectroscopy:

The absorbance spectrum of the supernatants was obtained using a UV-Vis spectrophotometer; between a wavelength of 200 nm and 700 nm. Spectra obtained were processed using software which is in-built in the spectrophotometer after data has been transferred to a computer as per the manufacturer's specifications[18].

HPLC analysis[19,14]:

The evaluation of the purified MAAs was done relative to their RP-HPLC profile using RP-HPLC system with Empower-2 software. The instrument was coupled with reverse-phase C18 column for the analysis.

Sample preparation of the extract was done by injecting 20 µl of the extract directly into the column *via* auto sampler. The samples (10 µl) were injected and the sample were analysed isocratically under a mobile phase of 0.02 % (v/v) acetic acid in HPLC-grade water at a flow rate of 1 ml/min. Measurements for MAAs were made at a fixed wavelength of 330 nm[20].

The individual peaks were thereafter scrutinized with the help of software provided by the manufacturer. The collected fractions were lyophilized and then characterized later.

Fourier Transform Infrared (FTIR) analysis:

Characterization of the functional groups in the MAAs was done using the FTIR analysis. The dried MAAs were blended with oven-dried Potassium bromide (KBr) to make a pellet using hydraulic press. The analysis was done using an FTIR spectrophotometer PerkinElmer. Spectra that were recorded were processed using the software that accompanies these devices from the manufacturer[21].

***In vitro* antioxidant assay:**

2, 2-Diphenyl-1-Picrylhydrazyl (DPPH) assay: 333 µl of DPPH was added to 1 ml of sample (concentration range: 20 to 100 µg/ml). L-Ascorbic acid was used as positive control. The mixture was shaken vigorously for a few seconds and then was allowed to stand at room temperature for 30 min. The absorbance was read at 513 nm in a UV-visible spectrophotometer. The absorbance of the reaction mixture is indirectly proportional to the free radical scavenging ability of the samples.

Scavenging effect (%)=(Absorbance of test-Absorbance of control)/(Absorbance of control)×100

Hydrogen peroxide (H_2O_2) inhibition assay: 43 mM solution of H_2O_2 in 0.1M phosphate buffer (pH 7.4) and the samples of varying concentrations (20 to 100 µg/ml) was mixed in equal volumes. L-Ascorbic acid was used as positive control. Sodium phosphate buffer without H_2O_2 served as blank. The samples were measured at 230 nm. The percentage of inhibition was calculated using the following formula,

H_2O_2 inhibition activity (%)=(Absorbance of test-Absorbance of control)/(Absorbance of control)×100

***In vitro* anticancer assay:**

The cytotoxicity of MAAs was studied on A431 (skin cancer cell line) and L929 (Fibroblast cell line) using (3-(4, 5-Dimethylthiazol-2-yl)-2,5 Diphenyl Tetrazolium Bromide (MTT) assay. Varying concentration of the sample (1 µg/ml to 500 µg/ml) were added to the cells (1×10^5 cells/well) and incubated for 24 h. Later 10 µg of MTT was added to each well and incubated again for 4 h. Finally, the entire media was aspirated without disturbing the formazan crystals to which 100 µl of Dimethyl Sulfoxide (DMSO) was added and mixed gently to dissolve the crystals. After 20 min the plate was read at 570 nm. The recorded absorbance was directly proportional to the cell viability. The half maximal inhibitory concentration (IC_{50}) value was calculated using GraphPad prism software.

RESULTS AND DISCUSSION

MAAs containing methanolic extracts of *Oscillatoria* sp. strain were detected using the absorbance spectra of the compound in the UV-Vis region and is illustrated in the fig. 1. The presence of MAAs in the organism was validated by the absorption peak shown by the spectrum which ranged between 334 and 335 nm.

Moreover, the spectrum showed typical peaks representing carotenoids (440-480 nm). The presence of such various pigments in the methanolic extract of *Oscillatoria* sp., is assisted by this work.

Thus, there are differences in the HPLC pattern and molecular properties of MAAs isolated from cyanobacterium *Oscillatoria* sp., presented below. The MAAs isolated are Palythene ($C_{13}H_{20}N_2O_5$ M/Z=284.1), Asterina-330 ($C_{12}H_{20}N_2O_6$ M/Z=288.2) Palythinol ($C_{13}H_{23}N_2O_6$ M/Z=303.1) and Porphyra-334 ($C_{14}H_{22}N_2O_8$ M/Z=345.3 In these, porphyra-334 has the highest molecular weight indicating its larger structure may be partly responsible for the improvement of its ability to absorb UV radiation (fig. 2). On the other hand, palythene had the lowest M.W consistent with giving it a simpler molecular structure for distinct purposes.

These differences in molecular structures of these MAAs indicate their different chemical functions and functions related to the protection against the UV induced oxidative damage. It is suggested that owing to the increased molecular weights compared to palythene and asterina-330, Porphyra-334 and palythinol would possess superior stability and antioxidative activity. The high separation efficiency of the reverse-phase HPLC system shows the strong

analytical method as applied to the identification of these compounds showing high molecular weight and polarity differences. Detailed characterisation of MAAs has given an understanding on the possibility of these components in pharmacological and cosmeceutical industries, noting their significance in protection against UV radiation and oxidative stress.

FTIR indicators for MAA derivatives are presented in the following table, with the solid line representing characteristic absorption peaks corresponding to key functional groups (fig. 3). A peak at 3399.22 cm^{-1} is assigned to the N-H stretch confirming the presence of primary or secondary amines. C-H stretch in the region 2968.00–2853.74 cm^{-1} corresponds to the region of alkanes the region 2350.00–2215.78 cm-1 corresponds to O-H stretch primary and secondary alcohols. A peak at 1650.23 cm^{-1} is assigned to the C=C stretch, a feature present in alkenes and the range 1454.96-1412.32 cm^{-1} refers to the aromatic C-C stretch, another feature of aromatic compounds. All these peaks collectively proved the existence of amines, alkanes, alkenes, and aromatic groups in MAAs and give an elaborate analysis of the chemical structure.

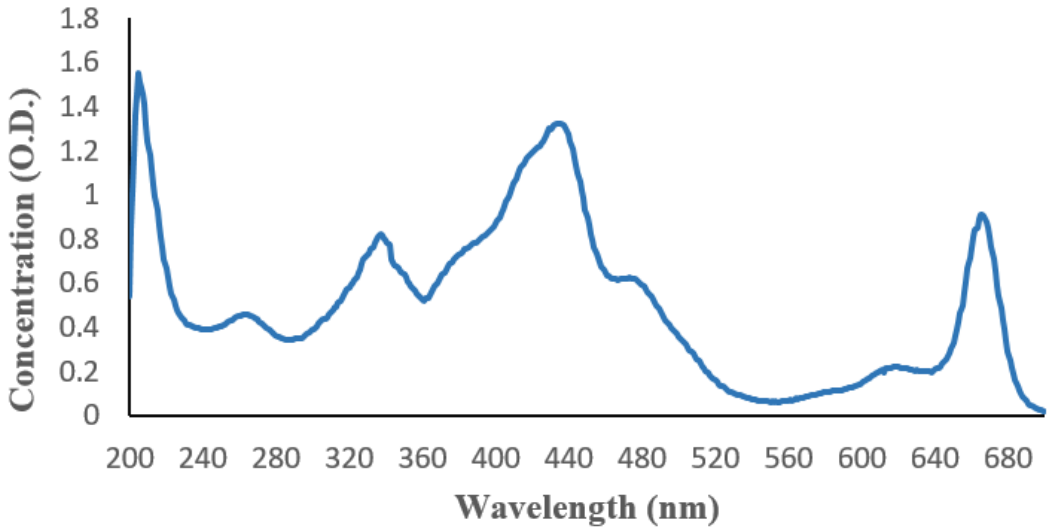

Fig. 1: Extraction of MAAs by UV visible spectrophotometry

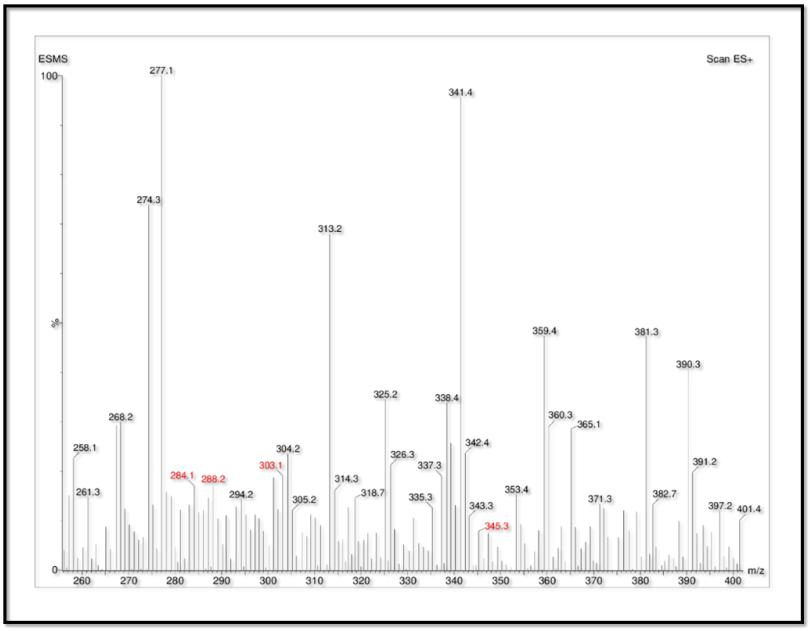

Fig. 2: Characterization of MAAs by HPLC

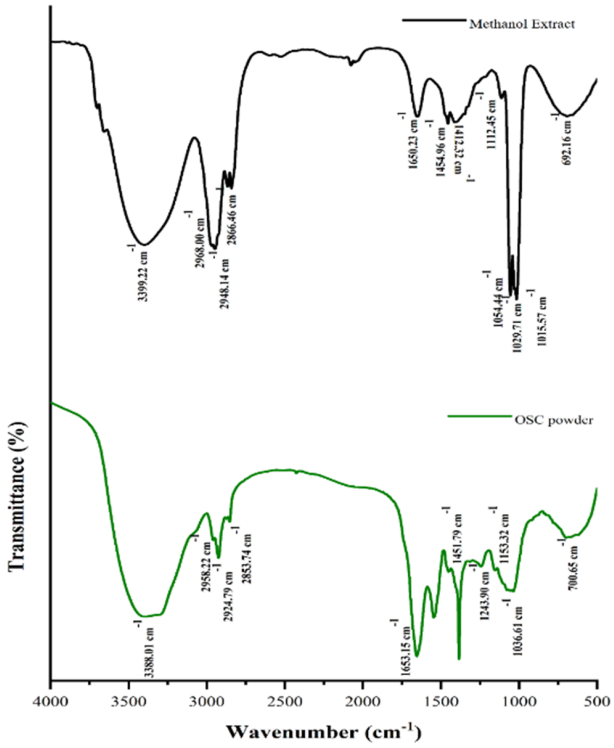

Fig. 3: FTIR analysis

The antioxidant ability of the samples was studied using different assays. The free radical scavenging ability of the sample was found to increase in a dose dependant manner in comparison with the standard used whose IC_{50} was found to be below 40 µg/ml. The IC_{50} of the sample in DPPH assay was found to be 80 µg/ml whereas in H_2O_2 assay it was found to be 100 µg/ml (fig. 4 and fig. 5).

Cell survival analysis by the MTT assay showed that MAAs were toxic to cancer cell lines, reducing their viability at an IC50 concentration of 47.43 µg/ml. This value implies that at low concentrations, MAAs displayed a highly effective cytotoxicity against A431 cell lines. The compound of interest did not exhibit any cytotoxicity on the normal cell lines used for the study.

Furthermore, a significant cytotoxic effect in a dose dependent manner was found. It can be observed from the fig. 6 that; as the concentration of MAAs rose, cell viability dropped notably especially when the concentration exceeded 200 µg/ml. This suggests that increased levels of MAAs lead to even greater levels of cytotoxicity thus making them useful as therapeutic agents in cancer. The obtained results suggest that MAAs can be potentially beneficial for further exploration as part of anticancer agents.

Cyanobacteria has evolved as strong potential sources of bioactive metabolites including UV-absorbing agents-MAAs. Of these, the *Oscillatoria* species have particular importance as they contain a range of pigments along with MAAs exhibiting photo-protective and antioxidant properties[18]. This discussion critically assesses the information obtained on *Oscillatoria* sp. against the background of closely related *Lyngbya* sp. strain HKAR-15 and correlates the novel findings of the study.

The UV-Vis spectral analysis of *Oscillatoria* sp. showed maximum absorbance at 334 nm which corresponds to the absorbance of MAAs. This observation confirms the presence of UV-screening compounds in this species. Also, in the upwards scan the shoulder was observed in the range of 440-480 nm due to the presence of carotenoids[22]. Apart from photo protection, these pigments are also involved in antioxidative defense systems of organisms. The presence of such peaks proves the ability of *Oscillatoria* sp. in synthesizing a number of pigments which gives an organism many-fold protection against UV radiation[1].

In contrast, *Lyngbya* sp. strain HKAR-15 showed specific MAA-related wavelengths of around 315–340 nm and additional peaks for carotenoids (around

470 nm) chlorophyll 'a' (around 420 and 665 nm) and phycobiliproteins (around 616 nm). Although both species synthesize MAAs and carotenoids pigments, the range of pigments in *Oscillatoria* sp. suggests that it was capable of photoprotection and photosynthesis under different conditions[23,24].

The *Oscillatoria* sp. was further analysed using HPLC that led to the recognition of various MAAs including; palythene (MW=284.1 Da), asterina-330 (MW=288.2 Da), polythinol (MW=303.1 Da) and porphyra 334 (MW=345.3 Da). Of the presented ones, porphyra-334 had the highest molecular weight, its structure being composed of two substructures, thus possessing enhanced functions of UV absorption[10]. Although palythene molecular weight is higher, its structural formula seems to be less complex rendering them perfect for specific biochemical functions.

Lyngbya sp. also exhibited a similar trend, with HPLC analysis revealing palythine (245.02) and porphyra-334 (347.1) as the most abundant MAAs. These findings are further supported by molecular profiling conducted in *Oscillatoria* sp., highlighting a shared biochemical strategy among cyanobacteria for MAA biosynthesis. Notably, *Oscillatoria* species demonstrated a broader spectrum of MAAs, suggesting a robust adaptive mechanism to varying UV radiation conditions. Based on these advantages, *Oscillatoria* species were selected for further investigation[8].

The functional group of *Oscillatoria* sp. shown by the FTIR analysis includes N-H stretch corresponding to primary and secondary amine, C-H corresponding to alkanes and C=C corresponding to aromatic amines. These findings confirm the richness of the chemical composition of its MAAs, which play the role of a photo protector[18].

But in the case of *Lyngbya* sp., complements information regarding the MAA structures was obtained from the respective NMR analysis. The presence of hydroxyl, carboxyl, and imine confirmed the structural as well as the functional nature of its MAAs. By comparing the functional groups of both species, it is pointed out that, although both species are similar, the detailed characterization of *Lyngbya* sp. corresponds to advanced methodologies that could be used for characterizing *Oscillatoria* sp. to extent.

Oscillatoria sp. grown under UV radiation exposure showed enhanced biosynthesis of MAAs as indicated by the higher absorption peaks of the UV-Vis spectrum of the algae. They acquired this flexibility of response in order to survive in regions where UV light is particularly intense. The capacity to synthesise porphyra-334 under stress conditions enables them to counteract UV induced oxidative stress[8].

Likewise, under supplemented UV-A and UV-B radiation, *Lyngbya* sp. exhibited enhanced MAA production, namely palythine and porphyra content four to five times with improved photoprotective mechanisms. Given the extensive UV induced biosynthesis capability of *Oscillatoria*, the comparative detailed quantitative data available only for *Lyngbya* sp., will help provide a complete appreciation of *Oscillatoria* full biosynthetic capabilities[19].

Although evidence suggests that the MAAs produced by *Oscillatoria* sp. possess potent antioxidant properties, quantitative evaluations remain limited. In addition, the presence of carotenoids further enhances its antioxidative defense by protecting cellular components from UV-induced damage[5]. The synergistic interaction between MAAs and carotenoids contributes significantly to natural photo protection, reinforcing the potential application of *Oscillatoria* sp. in UV-protective formulations[7].

Although the available literatures demonstrate the qualitative antioxidant property of the MAA's produced by *Oscillatoria* sp., their quantification studies are scarce. As the *Oscillatoria* sp. also possess carotenoids their antioxidant potential could be accelerated to a better extent. This synergistic compound activity can provide improved photo protection to the cellular components against UV radiation.

On the other hand, *Lyngbya* sp. had a dose-dependent radical scavenging capacity that equalled 70 % of antioxidant activity at a 1 mg/ml concentration of DPPH. Furthermore, the decrease in the intracellular ROS levels in UV-induced cells on treatment with MAAs proved that they protect against photodamage[2,7,4]. Based on these observations it appears that *Oscillatoria* sp. might as well possess similar or even better potentials when studied thoroughly using antioxidant tests. MAAs isolated from *Oscillatoria* sp. portrayed potent dose dependant cytotoxic activity against the cancer cells without harming the normal cells with an IC_{50} of 47.43 µg/ml. This suggest that it could be used as a safe therapeutic adjuvant in cancer treatment.

While anticancer research works done on *Lyngbya* sp. are not many, given its potent radical scavenging ability, it suggests that it can be used to treat diseases caused by oxidative stress including cancer. Further studies on *Oscillatoria* sp. MAAs should elucidate data from anticancer exploration, which could be supplementary to the results of the *Oscillatoria* sp.,[6].

Oscillatoria sp. holds a versatile and diverse application in regards to UV shield and antioxidant efficacy. Only the Africanized fruit fly has been found to generate a diverse product of MAAs and carotenoids, the seeming capacity to adapt to UV-saturated climes. Still, similar and in some cases, even better PAs and significantly higher photocprotective capacity of *Lyngbya* sp., together with specific pigment composition and structural versatility of *Oscillatoria* indicate this genus being equally suitable for further studies and biotechnological utilization. Sophisticated quantitative and qualitative analyses and characterization, as done for *Lyngbya* sp., may allow the routing use of *Oscillatoria* sp. And its secondary metabolites in pharmaceutical, cosmeceutical, and natural sun protection industries.

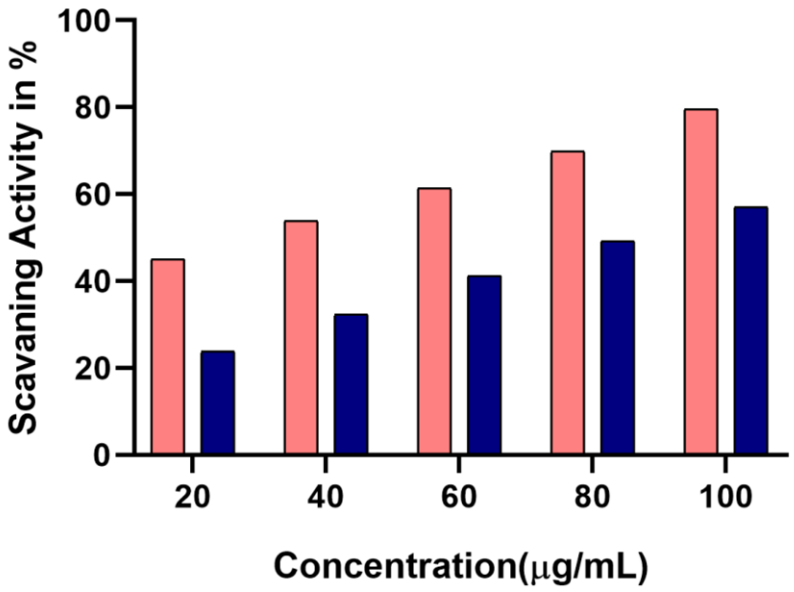

Fig. 4: Antioxidant activity using DPPH assay
Note: ( ): Control and ( ): Sample

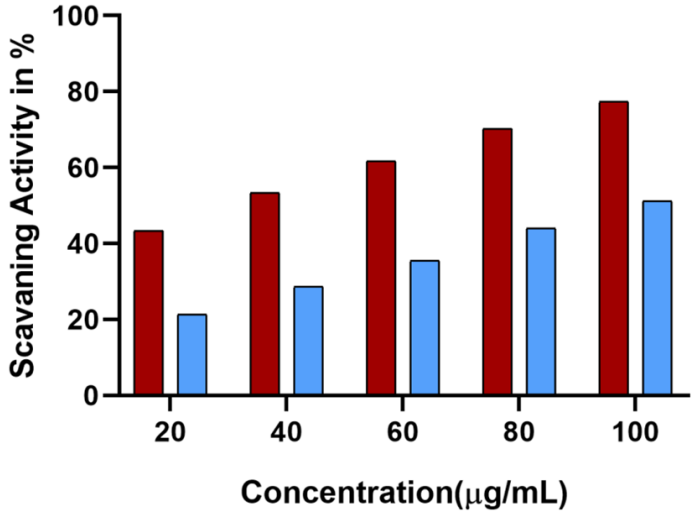

Fig. 5: Antioxidant activity using H_2O_2 assay
Note: ( ): Control and ( ): Sample

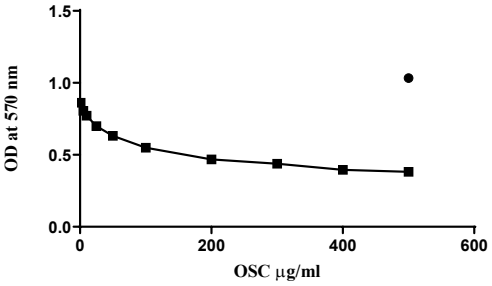

Fig. 6: *In vitro* cytotoxic activity against A431 cells
Note: ( ): Control and ( ): OSC µg/ml

Conflict of interests:

The authors declared no conflict of interests.

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