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ANTIOXIDANT, ANTI-ANGIOGENIC AND CYTOTOXIC EFFECT OF *ALOE BARBADENSIS*, A MEDICINAL PLANT FROM INDIA

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Keywords:

Aloe barbadensis (AB), AB methanolic root extract (ABMRE) Antioxidant, Antiangiogenic, cytotoxic, Migration

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ABSTRACT: Background: *Aloe barbadensis* (AB) is a member of the Liliaceae family, traditionally used for thousands of years in some parts of India and well known for its anti-inflammatory, antimicrobial, and wound healing properties. The purpose of the study is to evaluate the antioxidant, anti-angiogenic and antiproliferative effect of AB methanolic root extract on A549 lung cancer cell line. **Methods:** The Antioxidant activity of AB methanolic root extract (ABMRE) was tested using DPPH. The antiproliferative effect against A549-lung cancer cell lines was tested following MTT assay and their anti-migratory activity was tested by performing wound healing or scratch assay. Antiangiogenic property of root extract was determined by measuring the expression of VEGF protein in lung cancer cell by immunoblot technique and *in-vivo* CAM assay. **Results:** The ABMRE inhibited DPPH radical up to 50% at the concentration of 60 ± 0.04 µg/ml having high phenol content of 247.50 ± 21.39 mg GAE/g. The cytotoxic effect of ABMRE against A549 cells and their IC_{50} values were 7.429 ± 0.559, 5.370 ± 0.693, 3.52 ± 0.637 µg/ml for 24, 48, and 72 h respectively. ABMRE inhibited the migration of A549 cells in the wound healing assay was observed. The reduced expression of VEGF protein and inhibition of blood vessel formation in CAM assay by ABMRE was observed. **Conclusion:** The ABMRE showed antioxidant, antiproliferative, and anti-angiogenic activity could be evaluated further to identify different bioactive compounds having antineoplastic effects as a potential anti-cancer drug for treating lung cancer.

INTRODUCTION: Lung Cancer is the most common cancer type and is responsible for a large number of deaths worldwide.

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Cancer metastasis and a high incidence of recurrence in lung cancer lead to drug resistance and severe side effects. For the past 5 decades, various approaches have been used to improve cancer treatment along with the chemotherapeutic agents from natural products or natural products derived [1]. The phytochemicals from medicinal plants have made a reasonable contribution to developing anti-cancer drugs of different types [2]. Plant of genus AB is a monocotyledonous plant, belonging to family Asphodelaceae, reported to

have many bioactive compounds and bioactivities including antioxidant, antimicrobial, antifungal, cytotoxic, anti-parasitic, immunostimulant, anti-inflammatory and anti-cancer [3, 8]. The phytochemical profile of AB contains different secondary metabolites like anthraquinones, polyphenols, lignin, saponins, sterols, amino acids, and salicylic acid [9]. About 5% or above of oxygen inhaled during the process of respiration is converted to the reactive oxygen species (ROS) that includes O_2-, H_2O_2 and OH radicals [10]. The free radicals formed and their oxygen species are recognized as causative agents of pathogenesis.

The pathological conditions caused by these agents include age-related disorders, cardiovascular diseases, cancer, inflammatory diseases, and pathological neovascularization. The imbalance between the formed Reactive Oxygen Species (ROS) and the mechanism of antioxidant lead to oxidative stress, thus disturbing the homeostasis of an organism [11]. The reactive oxygen species (ROS) apart from inducing pathological condition, it also plays a vital role in disturbing the process of angiogenesis leading to the formation of new blood capillaries by the outgrowth or budding of preexisting vessels, including endogenous growth factors, cell migration and capillary tube formation [12, 13].

Angiogenesis is a positive player in many physiological conditions like wound healing, embryogenesis, menstrual cycle, and their abnormality can lead to a condition termed Angiogenic dependent diseases. Their prolonged mechanism can lead to pathological conditions like rheumatoid arthritis, diabetic retinopathy, or cancer progression (neoplastic tumors) [14]. In malignant tumors, angiogenesis is considered an important portal for their growth and metastasis. Often cancer angiogenesis and their vital mitogen VEGF (Vascular Endothelial Growth Factor) is targeted for the prevention and treatment of cancer [15]. The problems of cytotoxicity and chemoresistance associated with cancer treatment can be overcome by an anti-angiogenic approach. The mechanism of tumor angiogenesis which includes the supply of blood, nutrients, and growth factors to the developing tumor, is targeted using anti-angiogenic drugs [16]. With this background, the current study was designed to evaluate the antioxidant, anti-angiogenic and cytotoxic activity of the root extract of AB. This study might be the first to report the medicinal properties of the extract prepared from the root of AB plant collected from the southern part of India.

MATERIALS AND METHODS:

Collection of Plant Material: Fresh roots of AB collected from Namakkal city - India, in the sterile plastic bag and stored in the refrigerator. The taxonomic authentication of all the plants was carried out at the K. S. Rangasamy College of technology and deposited at the herbarium of the institute. The roots were washed thoroughly with the running tap water containing detergent to remove the soil and debris. The washed roots were then cut into small pieces and washed with distilled water and disinfectants (Tween 80).

Preparation of Plant Extract: The plant material cut in pieces were dried at room temperature and then grounded into a powder using a mechanical grinder. The grounded powder of 100 g was weighed and macerated by soaking in 250 ml of methanol and kept in a shaker for 72 h in shaker at 50 rpm at room temperature (32 ºC). The extract was filtered using Whatman filter paper No. 1 and concentrated using a rotary evaporator (Buchi, USA) at the temperature 45 ºC under reduced pressure and further dried overnight at 45 °C to dry powder. The dried AB methanolic root extract (ABMRE) was weighed, and the stock solutions of 10 mg/ml in 100% dimethyl sulfoxide (DMSO) were prepared and stored at 4 °C.

Determination of Total Phenols: Total phenols content in ABMRE was determined by a colorimetric method [17] with little modification using Folin-ciocalteau reagent. ABMRE of 1 mg/ml was prepared in methanol, and 100 µl of the extract was added separately to 750 µl of Folin-Ciocalteau phenol reagent and incubated for 5 min in the dark at room temperature. After the incubation, 750 µl of sodium bicarbonate solution (60 g/l) was added and incubated at 30 °C in the dark for 90 min. The absorbance was measured at 725 nm using a Bio-Rad Microplate absorbance reader. Gallic acid was used (5-80 µg/ml) to construct the standard calibration curve. The results were expressed as Gallic acid equivalents per 100 mg of extract (mg GAE/100 mg).

Free-Radical Scavenging Activity: The antioxidant activity of the extracts was assessed based on their ability to scavenge the stable 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical as described previously [18] with some modifications. Various concentrations of the extracts in methanol were prepared (20 - 100 µg/ml). A methanolic solution of DPPH 0.1 mM was prepared in methanol and rapidly mixed with different concentrations of the plant extract in a test tube (20, 40, 60, 80 and 100 µg/ml), with methanol serving as the blank sample, and control was also assayed simultaneously.

The contents of the tubes were swirled then allowed to stand for 30 min at room temperature in the dark. The absorbance was measured at 517 nm in a spectrophotometer. The scavenging ability of the plant extract was calculated using this equation:

DPPH scavenging activity (%) = Abs control-Abs sample / Abs control) × 100

Where, Abs control is the absorbance of DPPH + methanol; Abs sample is the absorbance of DPPH radical + sample (sample or standard). The EC_{50} value (µg/mL), the effective concentration at which DPPH• radicals are scavenged by 50%, was determined graphically. The total antioxidant activity was expressed as ascorbic acid equivalent/g dry extract. The assay was done in triplicates.

Cell Culture: A human lung cancer cell line (A549) was procured from NCCS, Pune was cultured in DMEM medium containing 1% antibiotic mixture (Penicillin, Streptomycin, and Ampicillin 100 units/ml) and supplemented with 10% fetal bovine serum. Cells were incubated at 37 °C in 5% CO_2 humidified incubator. Cells were passaged every 2-3 days using 0.25% trypsin-EDTA.

Cytotoxicity Assay: The cytotoxic activity of AB root extract was determined using MTT (3-[4, 5-dimethylthiazol-2-yl] -2, 5- diphenyltetrazolium bromide) a mitochondrial toxicity assay was carried out.

A 549 cells were seeded at a density of 5000 cells/well in a 96-well plate and allowed to attach overnight. The root extracts were diluted of volume 100 µl using DMEM at concentration ranges from 0-10 µg/ml. The cultured cell plates were exposed to the extracts and incubated for 24, 48 and 72 h at 37 ºC and 5% CO_2. Briefly, cells treated with the plant extracts were exposed to tetrazolium MTT at a 5 mg/ml concentration. Viable active cells reduced yellow MTT salt to insoluble purple formazan, which was dissolved using DMSO. The absorbance of the coloured solution was measured at a wavelength of 570 nm using a microplate spectrophotometer (Bio-Rad).

The obtained absorbance at 570 nm of both control and treated cells was used to calculate the percentage of cell viability. Assuming 100 % viability in control cells, the percentage of treated cells viability will be calculated accordingly:

Percent of viable cells = (Abs treated cell/Abs. pf control cells) × 100 Percent of Viable cells = (Abs. of treated cells/Abs. of control cells) × 100

Wound Healing Assay: To assess the ability of A549 cells to migrate after the treatment with AB, wound-healing assay was carried out in vitro. Cells were seeded at a density of 0.5×10^6/ well in 6-well plate and allowed to attach overnight. A scratch in the cell monolayer was made using a sterile plastic pipetting tip, and then the monolayer was washed with PBS.

The cells were treated with 0, 2.5, 5 and 10µg/ml of the extract. Images were taken at 24 h using bright-field microscopy (40 × magnification). An experiment was carried out in triplicates; data is representative of 3 random regions in each triplicate of each sample.

Immunoblotting: A549 cells were seeded at a density of 1×10^6 cells/ 100 mm plate and were then allowed to attach. The attached cells were treated with the given extract (AB) at the following doses (0, 2.5, 5 and 10µg/ml) and for 24 h. Whole-cell lysates were analyzed using 10% SDS polyacrylamide gel electrophoresis.

Proteins were transferred onto PVDF membranes before incubation with primary antibodies (VEGF (Cell signaling technologies) and GAPDH (Abcam) as a loading control. All protein bands were detected using a respective secondary antibody *via* enhanced chemiluminescence (ECL) detection system.

Anti-angiogenic Activity: Anti-angiogenic activity was evaluated using Chick Chorioallantoic Membrane (CAM) as previously reported [19] with little modifications. Fertile white Leghorn chicken eggs (Gallus domesticus) were obtained from a local hatchery with 5- or 6-days incubation, sterilized with 70% ethanol, and incubated at 37 °C in incubator for 48 hours with 70-80% relative humidity. On day 2 of post-incubation, 3 mL of albumin were withdrawn to minimize adhesion of the shell membrane with CAM. A square window of 1 cm^2 was opened in the eggshell opposite the blunt edge and sealed with adhesive tape. The eggs were returned to the incubator after the injection of 100 µL of methanol extracts over the blood vessels of the embryo at least six eggs were used for each experiment. After 48 hours of incubation, the eggs are observed as for eggs treated with extracts. The eggs will have incubated until the blood vessels of the embryo reach inhibition of 100%.

RESULTS AND DISCUSSION: Phytochemicals derived from medicinal plants are considered to be a source of exogenous antioxidants having polyphenolic substances, mostly flavonoids and phenolic acid, that protect the cells from free radical damages involved in the development of chronic diseases such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The present study evaluates the antioxidant activity of indigenous folk plant AB from the southern part of India. The antiproliferative and anti-angiogenic effect of such plant extract was studied against human cancer cells A549 to find a correlation with the antioxidant activity of those extracts.

Plant Extraction: The phytochemicals from plants have been extracted using different solvent systems20. In this study, we used methanol as the extraction solvent. The leaf extract was concentrated by complete evaporation of methanol, and the w/w percent yield was estimated to be 17.4% based on the solvent used.

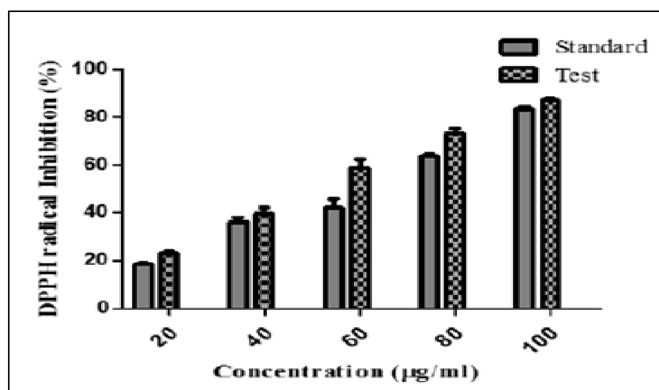


FIG. 1: DPPH SCAVENGING ACTIVITY (%) OF THE ABMRE AT DIFFERENT CONCENTRATIONS

DPPH Radical Scavenging Activity: The free radical scavenging property of ABMRE was evaluated by DPPH radical inhibition test. DPPH is a stable radical that can accept an electron or hydrogen radical and form a stable diamagnetic molecule and is one of the fastest tests available for investigating antioxidant activity of single antioxidants present in health-promoting antioxidant supplements [21].

The free radical scavenging effect of ABMRE was dose-dependent, ranged between (85.64±0.04) at 100 µg/ml to (22.78 ± 0.03) at 20 µg/ml **Fig. 1.** The values recorded for ABMRE were higher when compared to *A. vera* leaf methanolic extract [22]. The markedly higher DPPH scavenging capacity observed in ABMRE is most likely due to high antioxidant content in the root than the leaf. DPPH inhibitory or DPPH scavenging activity of 50% was observed at the concentration range of 60 ± 0.5 µg/ml, which had a significant negative correlation with the total phenolic contents. Accordingly, the antioxidant activity of ABMRE might be related to the contents of phenolic compounds [23, 24].

Total Phenolic Content: The total phenol contents in ABMRE were evaluated using the modified Folin-Ciocalteu assay, a very sensitive assay. The content of total phenol present in the ABMRE (**Table 1**).

TABLE 1: CORRELATION BETWEEN ANTIOXIDANT ACTIVITY OG ABMRE AND THE TOTAL PHENOL CONTENT

Plant	Part used	Solvent used	DPPH (IC_{50} in µg/ml)	Total phenols mg/s
Aloe barbadensis	Root	Methanol	6.14 ± 0.04	247.50 ± 21.39

Terms of gallic acid equivalent ranged from 247.50 ± 21.39 mg GAE/g of ABMRE. The antioxidant quality of polyphenolic compounds present in the plants prevents or reduces oxidative stress leads to chronic diseases such as cancer, cardiovascular diseases, diabetes, inflammation, infection [25]. In

recent studies, various polyphenols present in the Aloe vera extract attributed to reduced glucose uptake and prevented hyperglycemia [26].

Antiproliferative or Cytotoxic Effect of ABMRE against A549 cells: Against various cancer types, many chemo-preventive agents were used to produce side effects and prevent their extensive usage. It is imperative to develop much effective and less toxic drugs. Natural compounds from plants having anti-cancer properties discovered from various medicinal.

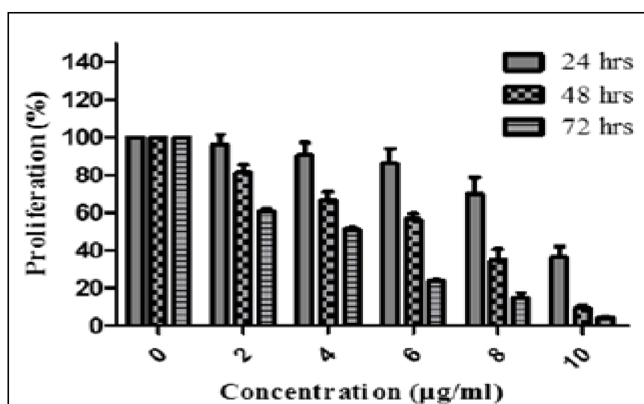


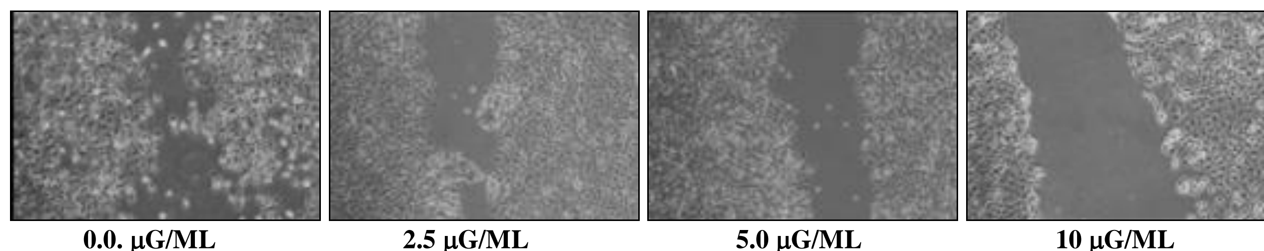
FIG. 2: ABMRE INHIBITS THE PROLIFERATION OF A549 LUNG CANCER CELLS. A549 cells were treated with 0, 2, 4, 6, 8 and 10µg/ml ABMRE for 24, 48 and 72 h. respectively. The proliferation rate was determined using an MTT assay. Values are expressed in µg/mL as means ± SD of (n=6) experiments (ANOVA-Bonferroni, $P < 0,001$ control vs treatment)

Plants and mushrooms [27] are derived from the traditional knowledge practiced in regions of different countries. Similarly, plants from the Indian tropical region having medicinal values used to treat cancer have not been clinically approved due to lack of scientific evidence through standard tentative procedures [28].

In the present study, the anti-cancer property of ABMRE was investigated. MTT assay was performed against the lung cancer cell line (A549). The ABMRE showed antiproliferative effect against lung cancer cell line (A549) showed the dose-response cytotoxic effect.

The calculated IC_{50} doses were 7.429 ± 0.559, 5.370 ± 0.693, 3.52 ± 0.637 for 24, 48, and 72 h, respectively, suggesting that the extract might have therapeutic potential against lung cancer cell lines. In **Fig. 2**, the graphical illustration of the dose-dependent antiproliferative effect of the active extracts against human lung cancer cell line. The results were on par with a previous study that reported that a compound isolated from *Aloe vera* resulted in time-and dose-dependent irreversible cell death of human lung non-small cell carcinoma (H460). Lee *et al.* reported that a compound from *Aloe vera* induced apoptosis in lung cancer by activating caspse-3 in a dose and time-dependent manner by increasing the release of nucleosome [29, 30].

ABMRE Inhibits the Migration Ability of A549 Cells: Advanced stages in cancers are due to metastasis formation that is fatal for cancer patients. The migration of cancer cells through the basement membrane and their vasculature with the target.



0.0. µG/ML 2.5 µG/ML 5.0 µG/ML 10 µG/ML

FIG. 3: WOUND HEALING ASSAY. A549 cells were scratched using a fine, sterile pipette tip to produce a narrow wound. The cells they were replaced with fresh medium containing different concentration of ABMRE (0, 2.5, 5, 7.5 and 10µg/ml) for 24 h. Images were captured after 24 h.

organs are termed as metastasis. Effective treatment for cancer will be the ability of the medicine to inhibit cancer cell migration. Cell migration is critically evaluated using the scratch wound assay in reference to the metastatic foci. To evaluate the cell migration inhibition effect of plant extract, a wound-healing assay was performed. The wound was repaired by A549 cells in untreated control wells. In contrast, inhibition of migration was clearly observed in wells with plant extract treated with different concentrations. The inhibition varies according to the different concentrations

(2.5, 5, 10 μg/ml) of the AB extract are shown in **Fig. 3**. Collectively, our data showed that ABMRE has an anti-migratory or wound-healing effect.

A similar effect was reported from *A. vera* extract that inhibited the migration and invasion of ovarian cancer [31].

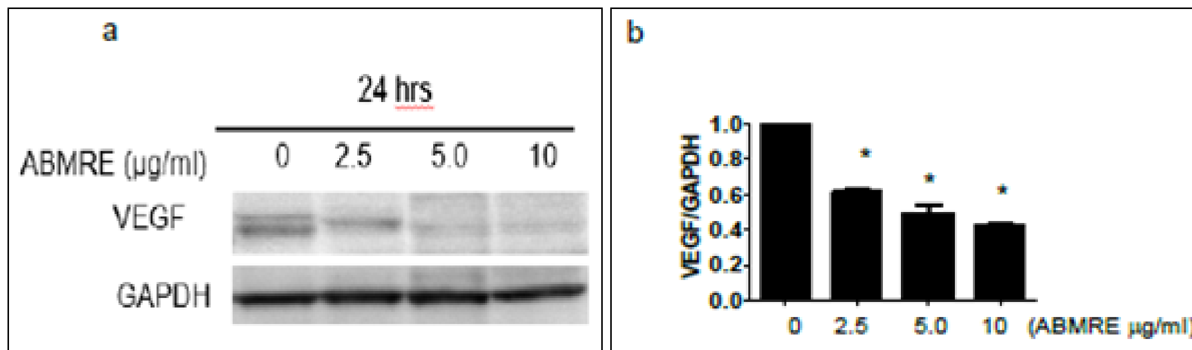
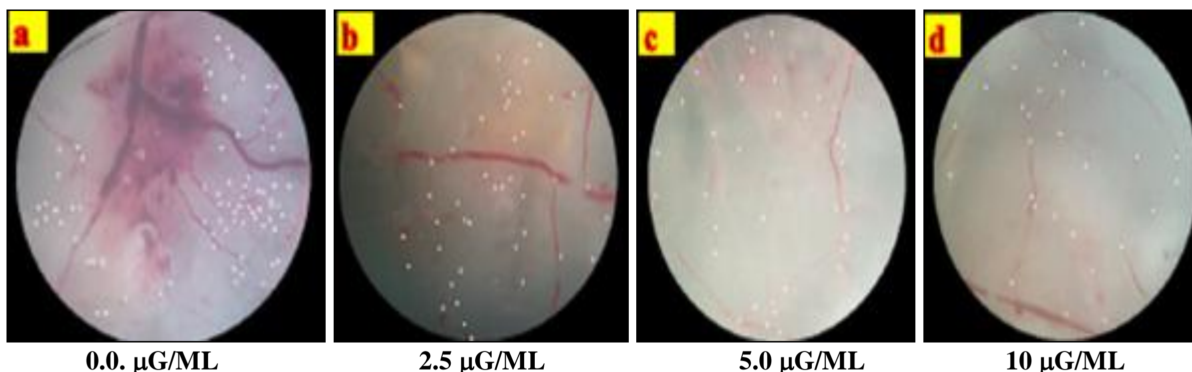


FIG. 4: ABMRE SUPPRESSES THE EXPRESSION OF VEGF PROTEIN. A549 cells were treated with different concentrations of ABMRE (0, 2.5, 5, 7.5, and 10μg/ml) for 24 h; the expression levels of VEGF are presented, with GAPDH as the control (a). Normalized expression levels of VEGF are presented in the right panel (b). *p<0.05 vs. control.

Antiangiogenetic Activity of ABMRE in A549 Cells: Angiogenesis is central to many physiological conditions and it is an essential step in solid tumor growth, invasion, and metastasis. Vascular endothelial cells modulation and their response to VEGF are signal proteins that induce the cells to proliferate, migrate and form new blood vessels [32]. Here, we demonstrated that the increased dose of AB extract inhibited the protein expression of VEGF **Fig. 4** and the result was consistent with an *in-vivo* CAM assay that showed the dose-dependent decrease in the number of vessel branches scored **Fig. 5**.

***In-vivo* CAM Assay:** Through *in-vivo* CAM model, the anti-angiogenic activity of Ab extract was tested. The number of blood vessels and the branches formed on CAM were scored before and after treatment. Based on the inhibition area around the applied disc, the blood vessels analysis was evaluated. The CAM treated with ABMRE showed distorted vascularization. The percentage of inhibition in ABMRE treated CAM was 59 ± 8.12, 41 ± 4.0, 30 ± 5.3 at the concentrations of 2.5, 5, and 10μg/ml, respectively. The average number of vessel branches formation scored in ABMRE treated CAM and in control CAM, respectively. The control of the blood vessels in the egg is shown in **Fig. 5**. Resveratrol, a type of natural polyphenol produced by several plants, demonstrated angiogenesis's inhibitory effect reduced endothelial cell growth in a dose-dependent manner in chick chorioallantoic membrane assay [33]. Scientific reports utter that the anti-angiogenic effect of the plants may be due to their antioxidant activity, credited by phenolics and flavonoids present in the respective extracts [34, 35]. Similarly, the anti-angiogenic effect of ABMRE may be due to their high antioxidant property collectively attributed to the presence of phenolic compounds present in the extract.



0.0. μG/ML 2.5 μG/ML 5.0 μG/ML 10 μG/ML

FIG. 5: *IN-VIVO* CAM ASSAY. Photomicrographs of CAM in the control and ABMRE treated samples. Control (a) and experimental samples treated with ABMRE at a concentration of 2.5 (b), 5 (c), 10 (d) μg/ml.

CONCLUSION: In conclusion, the ABMRE were found to effective medicinal plant with significant antioxidant, cytotoxic and anti-angiogenic effect. The ABMRE contains high phenolic content attributed to high DPPH scavenging activity and anti-angiogenic activity. Furthermore, apart from AB leaf for the first time, the beneficial effect of ABMRE was studied and added value to the importance of medicinal plants and justify the traditional use of medicinal plants. However, it is important to carry further studies to isolate the active compounds and to investigate the mode of action using *in-vivo* xenograft experimental tumor models to explore the role of these plants as a potential anti-cancer agent.

CONFLICTS OF INTEREST: The authors declared that there was no conflict of interest.

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