Research Article

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Anti angiogenic potential of Ajwa dates extract as a new novel for modulation of endothelial signaling pathways

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Abstract

The use of natural substances for prevention of neogenesis is a challenge and will be an advance in the vascular medicine. An example of abnormal vascular formation is infantile hemangioma.

Infantile hemangioma affect 4–10% of infants and affecting females more frequently than males (1,2).

Medical treatment with propranolol is commonly used for regression in the size of hemangioma. However, many side unwanted effects as hypotension and bradycardia are commonly seen.

This new challenge for usage of ajwa dates extract is effective in case of small and non deep sited hemangioma. This is beacause of the substances of Ajwa dates that are highly rich in antinfilamatory and antioxident substances.

Another substances in Ajwa dates have the properties of modulation and down regulation of hemangioma that will be discussed and will be clear.

Ajwa dates are rich in highly antioxidant and anti inflammatory substances as gallic acid and caffeic acid. The other substances as quercetin and ferulic acid are helpful for vascular protection and reduce the oxidative stress on the blood vesseles. Another important component for antimicrobal effect of Ajwa dates is the p -coumaric acid.

Keywords: Infantile hemangioma, Ajwa dates, angiogenesis, prophetic and alternative medicine.

Method of Preparation:

A- The Ajwa dates extract is prepared by extraction and different concentrations are used.

Step 1. Sample preparation:

Wash Ajwa dates with distilled water, remove the seeds and cut the flesh into small pieces. Use 40–45°C to dry the flesh parts then grind into a fine powder.

Step 2. Extraction:

Weigh 100 g of Ajwa powder then add 1 litter of 70% ethanol (1:10 w/v). keep at room temperature for 24–48 hours in the dark. Then filter through whatman No. 1 filter paper.

Step 3. Concentration

Remove ethanol using a rotary evaporator at ≤40°C. Freeze-dry or vacuum-dry the remaining aqueous fraction.Then store the dried extract at −20°C, protected from light.

Step 4. Stock solution for cell culture:

Dissolve the dried extract in sterile phosphate-buffered saline (PBS) then prepare a 100 mg/mL stock solution.

Step 5. Working concentrations:
Different concentrations are used : 25 µg/mL, 50 µg/mL, 100 µg/mL, 200 µg/mL

B- Human umbilical vein endothelial cells (HUVECs) are used. The 67assay, immunofluecence and microscopic examination are evaluated.

The value of this kind of cells is commercially available and widely used to study angiogenesis, oxidative stress, and VEGF signaling.

C- Culture conditions:

Supplements that used and added for cell culture include: Endothelial growth factors (e.g., VEGF, EGF, FGF) and Heparin are used. A cell viability assay for CCK-8 are used to asses the different concentration for better result.

Results:

There is marked reduction of endothelial cell proliferation. The cell proliferation is tested by the cell viability. The cell viability is decreased as confirmed by the use of CCK-8 assay and Ki-67 expression figure 1, 2.

For figure 1, The cell viability was expressed as a percentage of the untreated control. The ell viability decreased in a concentration-dependent manner. No significant differences were observed at 10 and 25 µg/mL, whereas significant reductions occurred at 50 and 100 µg/mL (*p < 0.05), 200 µg/mL (**p < 0.01), and 400–800 µg/mL (***p < 0.001). Data are presented as mean ± SD.

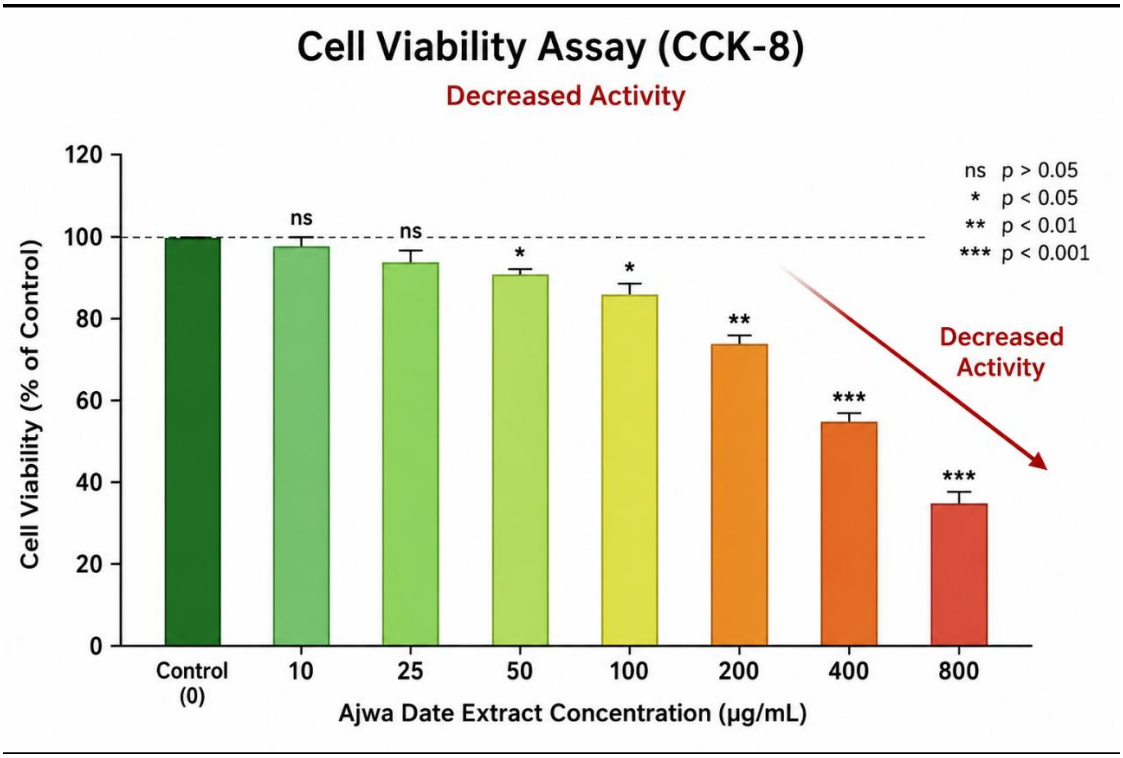

Figure 1: Shows effect of Ajwa date extract on cell viability measured by the CCK-8 assay. The cells were treated with increasing concentrations of Ajwa date extract (10–800 µg/mL).

The immunoassey is tested as seen in figure 2. In control group, strong nuclear Ki-67 immunoreactivity (green fluorescence) was observed, indicating a high proportion of actively proliferating cells. Treatment with increasing concentrations of Ajwa extract (25–200 µg/mL) progressively decreased the number and intensity of Ki-67-positive nuclei.

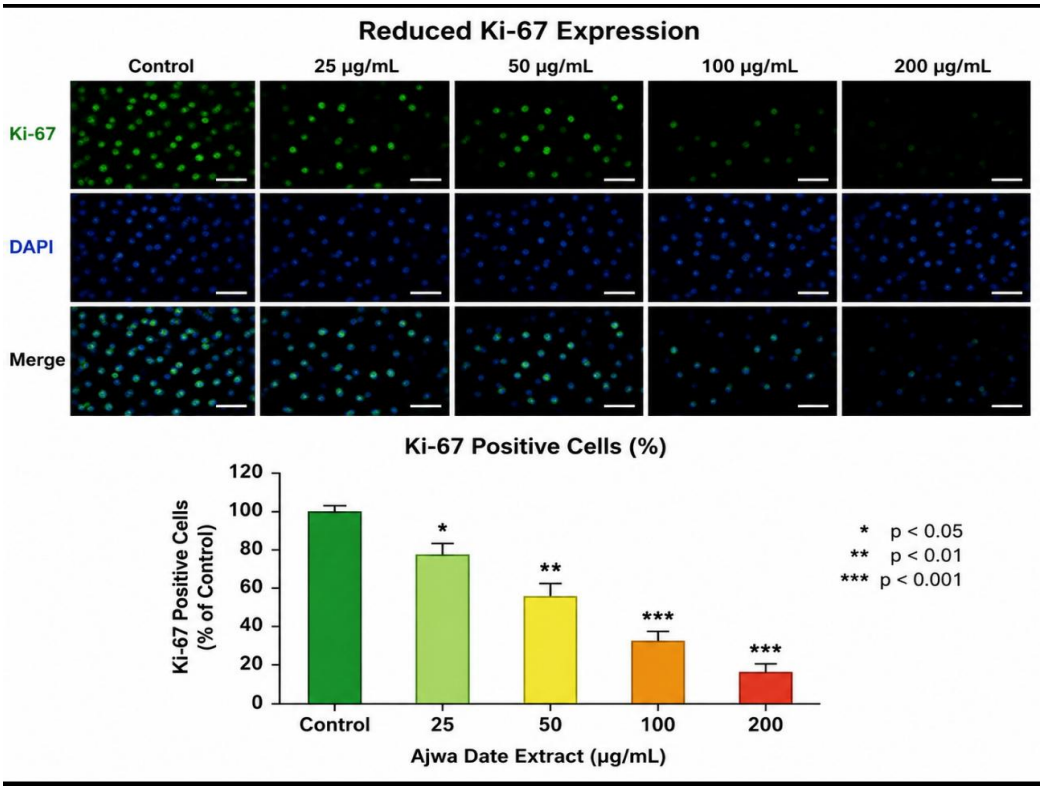

Figure 2: The immunofluorescence staining demonstrated a concentration-dependent reduction in Ki-67 expression in HUVECs following treatment with Ajwa date extract.

In contrast, DAPI staining (blue) is used to visualize total cell nuclei which is remained relatively constant across all groups. This indicating that the observed reduction in Ki-67 was primarily due to decreased cellular proliferation rather than loss of nuclei. Quantitative analysis confirmed a significant dose-dependent decline in Ki-67-positive cells, with the greatest inhibition observed at 100 and 200 µg/mL ($p < 0.001$).

The merged images demonstrate the co-localization of Ki-67-positive nuclei (green) with DAPI-stained nuclei (blue). In the control group, numerous nuclei exhibited strong Ki-67 immunofluorescence, indicating a high proportion of actively proliferating cells.

Microscopic examination of HUVECs treated with Ajwa date extract demonstrated a concentration and time-dependent inhibition of cell proliferation (Figure 3).

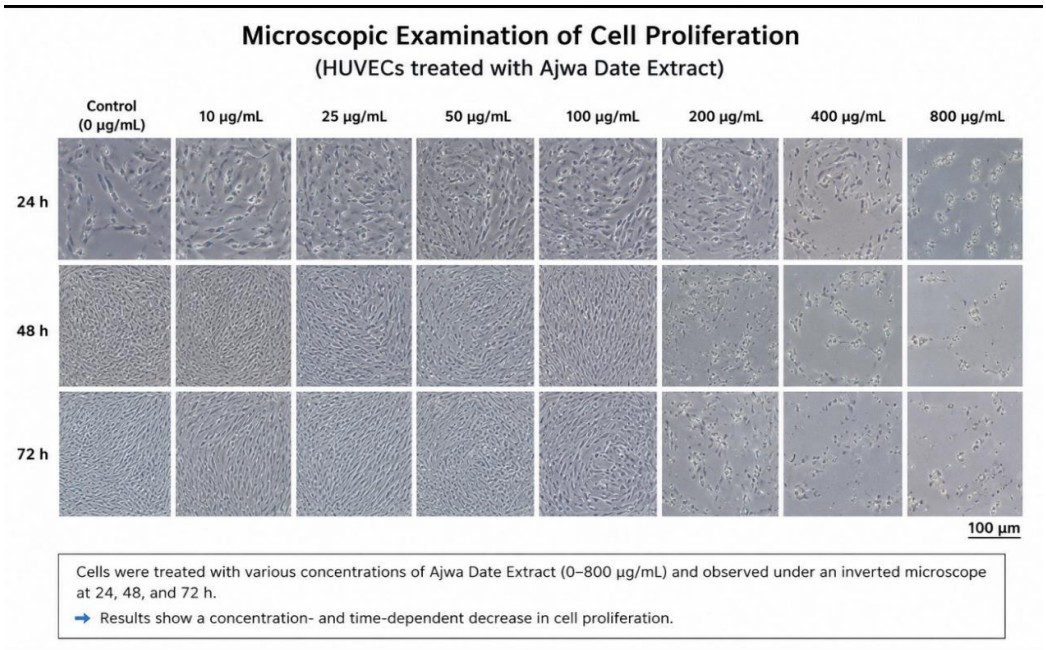

Figure 3: Microscopic examination of HUVECs treated with Ajwa date extract demonstrated a concentration and time-dependent inhibition of cell proliferation.

At low concentrations (10–100 μg/mL), cells largely retained their characteristic cobblestone morphology with only a slight reduction in cell density compared with the untreated control.

In contrast, treatment with higher concentrations (200–800 μg/mL) resulted in a marked decrease in cell confluence, accompanied by cell shrinkage, rounding, and partial detachment, indicating impaired proliferation and reduced cell viability.

These morphological changes became progressively more pronounced after 48 and 72 hours of exposure, suggesting that Ajwa extract exerts a sustained antiproliferative effect on endothelial cells.

Overall, the microscopic observations are consistent with a dose- and time-dependent suppression of HUVEC growth and support the quantitative findings obtained from cell viability assays CCK-8.

Discussion

Infantile hemangioma is a benign tumor in which rapid proliferation phase is happened. This phase is regulated by VEGF pathway result in abnormal endothelial cell proliferation. This abnormal angiogenesis is increased by exposure to hypoxia through dysregulated vascular signaling pathways (3–6).

The VEGFA–KDR (VEGFR2) is one of the signaling axis that activation result in acceleration of endothelial proliferation, migration and neo vascularization.

Another pathway is the PI3K/Akt and MAPK pathways result in VEGFA expression and activation of VEGFR2-mediated downstream signaling thereby promoting endothelial survival and vascular growth (5–7).

Ajwa dates are rich in gallic acid, quercetin, chlorogenic acid, caffeic acid, ferulic acid and p-coumaric acid. These substances are potent antinflamatory and antioxident properties that reduce intracellular reactive oxygen species, suppress NF-κB activation, decrease inflammatory cytokine production and improve endothelial function in experimental studies (1,8).

There are multifactorial effects of Ajwa dates that result in regression of the size of hemangioma. This effect is regulated by the frequency of application and method of follow up.

The selection criteria for the patient is important. One of the important criteria is age and size of the hemangioma. The best age is less than 6 month as there is limited time for hemagioma and no more proliferation is expected.

The hemangioma should be superficial and uncomplicated this means the size is less than 1 cm and not connected to deep structure. The effects is reduction of the endothelial cell proliferation which is confirmed by the use of CCK-8 assay and reduced Ki-67 expression.

Another effect through increasing apoptosis and supression angiogenesis this is confirmed by microscopic examination. For further researches the effect of VEGFA, KDR, (VEGFR2) and FLT4 (VEGFR3) are planed to be tested.

Referances

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