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Dendrosomal nano-curcumin reduces VEGF gene expression and with increasing cell apoptosis has an inhibitory effect on the Burkitt lymphoma cell line

Mahboobeh Cheragh [1], Majid Sadeghizadeh [2], Mohammad Hassan Pouriayevali [3], Masoud Parsania[4,5*]

1 Department of Microbiology, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
2 Department of Genetics, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran
3 Department of Arboviruses and Viral Hemorrhagic Fevers (National Reference Laboratory), Pasteur Institute of Iran, Tehran, Iran
4 Department of Microbiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
5 Medical Genomics Research Center, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

*Corresponding author: Department of Microbiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran. E-mail: mparsania@iautmu.ac.ir
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Abstract

Background: During research on lymphoma and its malignancies, scientists have traced the role of the angiogenesis index in patient survival. Epstein-Barr virus (EBV) is a human tumor-causing virus that targets B lymphocytes and causes persistent infection. This virus is also associated with malignancies, such as Burkitt's lymphoma. Using herbal medicines to treat cancer and angiogenesis has been considered, due to the side effects of chemical drugs. This experimentation aimed to research the antiviral impact of nano-curcumin on the Daudi cell line (which belongs to Burkitt's lymphoma) and to evaluate the expression of the vascular endothelial growth factor (VEGF) gene.

Materials and Methods: The cytotoxicity of nano curcumin, curcumin, and dendrosome on Daudi cells and normal human lymphocytes was evaluated using an MTT assay. Cellular apoptosis was assessed by Annexin / PI flow cytometry. The VEGF angiogenesis gene expression was performed by real-time PCR.

Results: The 50% cytotoxic concentration (CC50) was determined 30 µg/ml for dendrosomal nano-curcumin, 50 µg/ml for curcumin, and 987 µg/ml for dendrosome in the Daudi cell line.

Dendrosomal nano curcumin (DNC) caused time and dose-dependent death in Daudi cancer cells compared to curcumin. Dendrosome did not show toxicity on control cells. The results of Flow cytometry are constant with the results of the MTT test. The data obtained from the real-time PCR showed a significant decrease in the expression of the VEGF gene ($P < 0.01$).

Conclusion: The dendrosomal nano curcumin is involved in angiogenesis by reducing the expression of the VEGF gene, and can be a good candidate as a supplement drug in the chemotherapy treatment of Burkitt's lymphoma.

Keywords: Dendrosomal nano curcumin, Epstein-Barr virus, Daudi cell line, Anti-angiogenesis.

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1. Introduction

Burkitt's lymphoma (BL) is fast-growing cancer. There are three clinical types of Burkitt's lymphoma, which are endemic, sporadic, and immunodeficiency-associated, and in all clinical types of Burkitt's lymphoma, Epstein-Barr virus infection plays an important role in causing the disease. BL may affect the Lymph nodes, brain and spinal cord (central nervous system), intestines, kidneys, ovaries, and other organs and cause tumors of the jaw and mouth. Angiogenesis plays an important role in the spread of cancer and tumor metastasis. It has recently been shown that treatment of malignant lymphomas with anti-vascular endothelial growth factor (anti-VEGF) agents can increase cancer cell apoptosis and decrease blood vessels (1-3). Mainly the mortality rate in elderly patients is higher than in children, although, without timely treatment, Burkitt's

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lymphoma can be fatal in both age groups (4). Common treatments include radiotherapy, chemotherapy, and bone marrow transplants, which have many side effects (5).
Treatment of viral infections with available chemical and antiviral drugs causes mutations in some latent and lytic infections of the virus, which leads to treatment failure (6). Research and development of antiviral drugs based on herbs are a need for the treatment of BL (7). The usage of medicinal plants and nanotechnology to increase the efficiency of chemical compounds for the treatment of diseases are common in many developed and developing countries as a major way of treating cancer and malignancies (8).
Turmeric is the popular name for Curcuma longa, known in India as Haldi, and belongs to the ginger family. Curcumin has been used in traditional medicine for thousands of years (9). Recent studies have shown that this compound has antioxidant, anti-inflammatory, antibacterial, antiviral, antiproliferative, and pro-apoptotic effects and has tremendous therapeutic potential in cancer treatment. Despite its excellent healing properties, it is difficult to dissolve in water. Additionally, its stability and bioavailability are low; Today, to increase the solubility of this valuable substance in body fluids and consequently increase the anti-cancer effects of curcumin, various carriers are used to deliver the drug (10). Dendrosome is a new family of copolymer vectors that have been used in previous studies by this group to transfer genes into eukaryotic cells. The results of several studies have shown that dendrosomes have numerous benefits, such as stability, non-toxicity, and biodegradability (11). Dr. Sadeghizadeh and his colleagues at Tarbiat Modares University used nanotechnology methods to increase the biological availability of this compound and provided the dendrosomal nano-curcumin (DNC) (12-15).

In this study, we aimed to investigate the potential effect of DNC as an anti-angiogenesis compound on VEGF gene expression in the Daudi cell line as Burkitt's lymphoma cells.

Materials and Methods

Cell Culture

Daudi cells were purchased from the Pasteur Institute of Iran. RPMI 1640 (Gibco) culture medium with 10% fetal bovine serum (Gibco), 5% Co2, and 37 ° C was used for the culture and maintenance of the cells.

To isolate peripheral blood mononuclear cells (PBMCs) as controls, these cells were separated from a normal person using a Ficoll-lymphodex (inno-train) and were cultured at 15% bovine serum and RPMI 1640 at 37 ° C and 5% CO2 (16-18).

Preparation of nano curcumin

The method of preparation of nano curcumin has been described in our previous study (19). Briefly, different weight/weight ratios of dendrosome/curcumin ranging from 50:1 to 10:1 were analyzed, leading to establishing an appropriate ratio of 25:1. Highly pure curcumin was dissolved in various amounts of dendrosome and evaluated in terms of absorbance spectrum by UV spectrophotometry (BioTek Instruments, Inc) (20). The solution of curcumin/dendrosome was sterilized by using a 0.22 μm pore size syringe filter (Millex-LG, Millipore Co, USA). Finally, the prepared DNC was stored at 4 ° C without light exposure (21).

Cellular Cytotoxicity Test

The cytotoxicity effect of curcumin, dendrosome, and DNC was determined in Daudi and PBMCs by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide) test. Briefly, Daudi cells were first examined morphologically, and 30,000 cells were cultured in 96- well microplate wells. After 24 hours, the cells were treated with different concentrations of curcumin (100, 90, 80, 70, 60, 50, 40 ,30 ,20 ,10 μg/ml), dendrosome (1200, 1000, 800, 600 μg/ml) and dendrosomal nano curcumin (60, 50, 40, 30, 20, 10 μg/ml), in 200 μl of medium with 2% FBS serum in triplicates. After 72h incubation, the cells were centrifuged, and the medium was removed. 20 μl of MTT solution (0.005 g/ml PBS) and 80 μl of RPMI 1640 culture medium were added to the wells. After 4 hours of incubation at 37 °C and the formation of formazan crystals, 100 μl of dimethyl sulfoxide (DMSO; Sigma-Aldrich Co.) was added to each well. Three wells that contain only 100 μl DMSO as blank and three wells with100 μl culture medium without curcumin were considered as control. Finally, after 10 minutes, the absorbance of each well was measured at a wavelength of 540 to 630 nm.

The cytotoxicity of all three compounds on Daudi cancer cells as well as PBMCs was calculated using the formula below:

$$\textbf{Cytotoxicity}\ \% = 1 - \frac{Mean\ OD\ Test - Mean\ OD\ Blank}{Mean\ OD\ Control - Mean\ OD\ Blank} \times 100$$

The 50% cytotoxic concentration (CC50) was specified from the dose-response curve.

Flow Cytometry

Flow cytometry with Annexin-PI (BD FACS Calibur; Becton-Dickinson, USA) was used to evaluate the extent of cellular apoptosis. Daudi cells and normal cells were treated at 30 μg/ml concentration (CC50 nano curcumin per Daudi cells) at 72 h. After 72 h incubation; they were evaluated using an apoptosis detection kit (Ebioscience, Thermo Fisher Company) based on annexin PI according to the kit instructions.

RNA Extraction and cDNA Synthesis

Daudi cells were treated with different concentrations of DNC (40, 30, 20, 10 μg / ml) separately. After 72 hours, the complete RNA of the cell was extracted from cells using the FAVORGEN kit (Biotech Corp) according to the kit standard protocol. The RNA quantity was determined by UV spectrophotometry.

Reverse transcription of RNA was performed using a cDNA synthesis kit (Yektatajhiz azma) according to the instructions of the kit.

Quantitative real-time PCR

Quantitative measurement of VEGF and GAPDH (as an internal

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control) genes expressions was performed by real-time RT-PCR based on the comparative quantification method in LightCycler® 96 Instrument (Roche Molecular Systems Germany) using SYBR Green PCR master mix (Yektatajhiz azma) according to its manufacture instructions. The calculation of VEGF gene expression was carried out using the ΔΔCt method. The specific primers for VEGF and GAPDH genes are presented in (Table 1).

Statistical Analysis

Student t-test was used for statistical and significance analysis level calculation between the two groups, and an ANOVA test was used for more than two groups. Differences in gene expression using Genex 6 software and statistical analysis using SPSS 21 software and charting are made with graph pad prism 8. A p-value less than 0.01 was considered significant.

Gene	Primer sequence (5′→3′)	Product length (bp)
VEGF	F: ATCTGCATGGTGATG R: GGGCAGAATCATCACGAAGT	218
GAPDH	F: CTCTTGCTACTCTGCTCTG R: GCCTGCCTGGTGATAATC	179

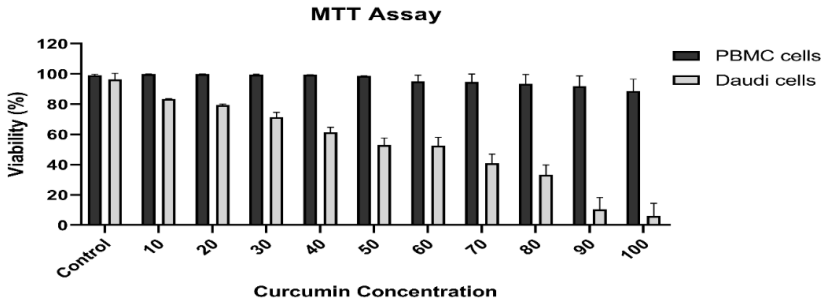
Table 1. Sequences of primers used for real-time PCR.

Results

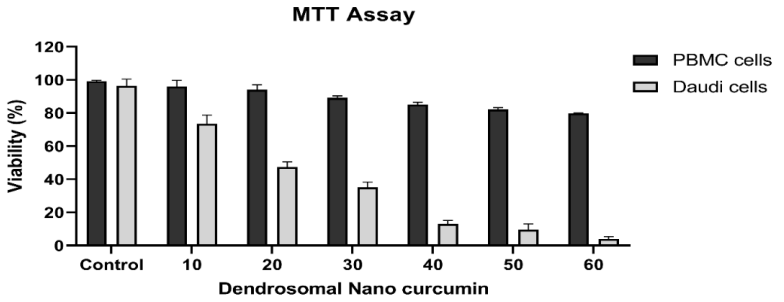
Cytotoxicity of curcumin, dendrosome, and DNC on Daudi and PBMCs

The CC50 of curcumin, dendrosome and DNC on Daudi and PBMCs was evaluated by MTT assay after 72 hours. MTT results of curcumin, dendrosome, and DNC treatments with different concentrations on Daudi and PBMCs are shown in figure 1. The CC50 value of DNC for the Daudi cell line within 72 hours was evaluated at 30 μg/ml and curcumin and dendrosome were determined at 50 μg/ml and 987 μg/ml respectively. Examination of MTT assay results showed that curcumin at 30 μg / ml did not have the same effect on cell death and cytotoxicity as DNC.

(A)



(B)



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(c)

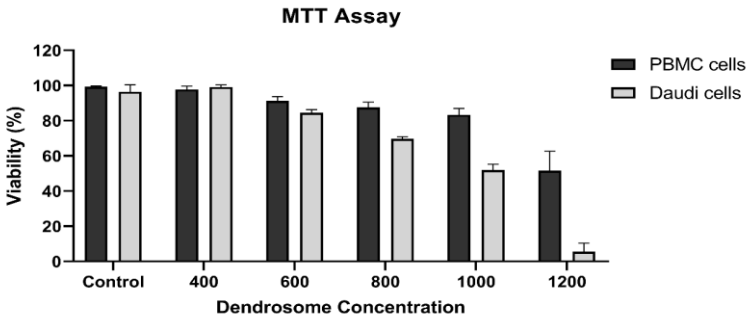

Figure 1. Comparison of CC50 obtained for curcumin, DNC, and dendrosome at 72 h MTT assay methods. (A) Effect of Curcumin on Daudi and PBMC, (B) effect of DNC on Daudi and PBMC cells, (C) effect of Dendrosome on Daudi and PBMCs. This graph indicates the average of three independent experiments. Error bars show standard deviation.

Apoptosis assay

The cell apoptosis effect of DNC on the Daudi cell line and PBMCs were examined by flow cytometry. Daudi and PBMCs were treated with a CC50 concentration of DNC. As shown in figure 2 DNC has an inhibitory effect on cancer cells but at the same concentration has no adverse impact on normal cells. The results of cell apoptosis by Annexin V/PI showed that the CC50 concentration of DNC on the Daudi cell line caused 32.5% early apoptosis and 10.3% late apoptosis and on normal cells caused 10.3% early apoptosis and 4.45% late apoptosis respectively.

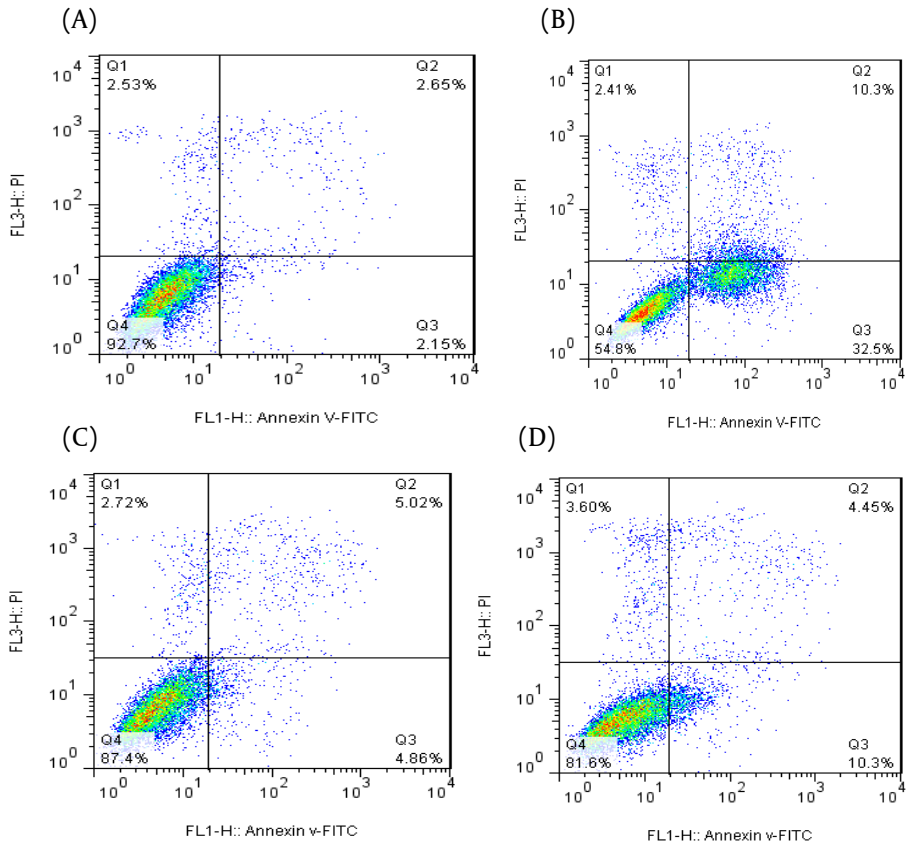

Figure 2. Flow cytometric diagram of Annexin/PI testing. (A) Daudi cell line untreated as control, (B) Daudi cell line treated by 30 µg/ml of DNC, (C) PBMCs line untreated as control, (D) PBMCs line treated by 30 µg/ml of DNC.

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Gene Expression by Real-time Quantitative PCR

VEGF gene expression was conducted by quantitative real-time PCR. The result of VEGF gene expression after treatment by different concentrations (10, 20, 30, and 40 μg/ml) of DNC, showed VEGF genes are dose-dependently inhibited by DNC (Figure 3). The results showed that in Daudi cells, VEGF expression decreased after 72h of DNC treatment. In PBMCs treated by DNC (In the above concentrations), the expression of the VEGF gene did not alter significantly.

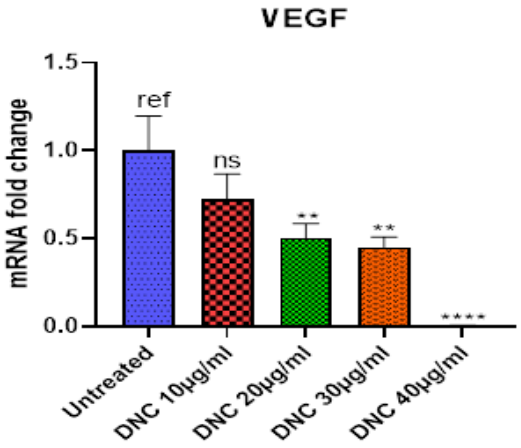

Figure 3. Gene expression of VEGF in Daudi cells after 72 h treatment. Significant decrease in down-regulation of VEGF genes at different concentrations compares to untreated control. The results are expressed as the significant (**< 0.01, ****P<0.0001). This graph indicates the average of three independent experiments. Error bars show standard deviation.

Discussion

During lymphoma research, the role of angiogenesis in cancer cell metastasis and reduced patient survival is evident. In different types of non-Hodgkin's lymphoma (NHL) B cells, angiogenesis may be one of the most critical factors in the development of invasive tumors. Given the importance of angiogenesis in the treatment of lymphoma cancer, targeting the angiogenesis gene (VEGF) is one of the most important therapeutic tools, which is based on preventing the formation of blood vessels around growing cancer cells (22-23). It is accepted that chemical antiviral drugs are most effective in overexpressing tumors. However, several clinical studies have shown that in different patients with the same tumors, the effectiveness of these drugs is not always enough. Therefore, the development of new treatment strategies based on natural nanotechnology seems to improve patient survival (24-26). In the current study, it was found that DNC can decrease VEGF gene expression in the Daudi Burkitt lymphoma cell line; therefore, it can affect prevent angiogenesis in Burkitt lymphoma. In this context, the DNC concentrations used to inhibit the growth of Daudi cancer cells had no harmful effect on normal lymphocytes (27-31). Treatment of Daudi cell line with different concentrations of DNC showed that DNC inhibits lymphoma cell proliferation in a dose-dependent manner by acting on cellular apoptosis. A previous study by Alizadeh and colleagues showed that chemical prevention of azoxymethane-induced colon cancer in rats is possible using a new polymer nanocarrier – curcumin (32-33). Another study by F. Wieser and colleagues has shown similar effects of curcumin on the inhibition of angiogenesis in vivo and in vitro. Curcumin can reduce VEGF expression in a laboratory model of endometriosis and inhibit angiogenesis induced by hypoxia in vitro (34, 35). In vivo studies show that curcumin inhibits angiogenesis by reducing the density of small blood vessels in Ehrlich ascites cancer (36). In other studies, researchers showed that curcumin is an angiogenesis inhibitor by downregulating VEGF in other diseases such as corneal diseases, diabetic retinopathy, diabetic nephropathy, and ectopic endometrium (37-41). Studies in cardiac patients have shown that curcumin is effective in reducing the expression of angiogenic genes in the aortic ring of diabetic patients (42). A previous clinical study showed that curcumin could reduce vasculogenic and angiogenesis in the pathological process of cancer (43). Another phase I trial revealed that curcumin combination with dendrosom could significantly decrease VEGF levels after three cycles of treatment (44). In another study, Zigang Cao and colleagues 2020 showed that nano curcumin inhibits angiogenesis in zebra fish by downregulating hifɪa/VEGF signaling pathway (45).

The DNC has induced the apoptosis process in the Daudi cell line in this study but has no significant effect on PBMCs. Several reasons explain why curcumin does not affect normal cells and induce apoptosis in cancer cells such as curcumin's effects on cell signaling pathways including cell proliferation and cell survival pathways, also caspase activation, and death receptor pathways, which are effective to induce apoptosis on tumor cells (46). According to our results, DNC can suppress VEGF expression in the Daudi cell line. Therefore, this drug has significant potential inhibition of angiogenesis, and it can candidate drug to use as a complement drug for Burkitt lymphoma treatment, but more investigations are necessary for this area.

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Footnotes

Conflict of interest: The authors have no known competing financial interests or personal relationships that affect the work reported in this article.

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