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In vitro anti-cancer potentiality of quince and dandelion leaves extract against leukemia cell lines and database retrieval expression of *BCR ABL* and *TCR* genes in leukemia

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Abstract

Introduction: Plants were used in medicine to treat various diseases long ago, but data on aqueous extracts of quince and dandelion are currently very limited.
Objectives: *In vitro* cytotoxic impacts of aqueous quince and dandelion leaf extracts on leukemia cell lines (Jurkat and K562) were investigated. In addition, the average levels of *BCR, ABL* and *TCR* gene expression were studied.
Materials and Methods: In current *in vitro* experimental study, quince and dandelion leaves were extracted via aqueous extraction. Stock extracts (50 mg/mL) were prepared by dissolving 50 mg of aqueous extracts in 1 mL of 10% DMSO and filtering them. Two doses (0.5 and 5 mg/mL) of each extract were subsequently used to determine its cytotoxicity to Jurkat and K562 cells via flow cytometry *in vitro* killing assay. For genetic studies, the expression levels of the BCR, ABL and TCR genes were retrieved from the gene expression database of normal and tumor tissues 2 (GENT2).
Results: The number of killed cells significantly increased when Jurkat and K562 cells were treated with 5 mg/mL dose of quince and dandelion leaf extracts. In the genetic study, the average expression level of *BCR ABL* was significantly greater in blood samples from patients with cancer than in those from healthy controls. However, TCR expression did not significantly differ.
Conclusion: These results highlight the cytotoxicity of both leaf extracts, mainly dandelion, to leukemic cells. Additionally, the expression of *BCR ABL* in blood cancer should be emphasized.

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Introduction

Plants are essential to human health, and it is widely documented that a diet high in plant-based foods is related with a poorer threat of degenerative diseases, including cancer. Numerous plant-derived compounds have been isolated that display activity against various cancer cell types. An increased intake of vegetables and fruits has a role in supporting a healthy state and preventing diseases, including cancer (1). Therefore, medicinal plants play important roles in human health because of their many chemical components and biological activities. Quince and dandelion are two of these plants that are well known for their numerous health benefits.

Quince (*Cydonia oblonga)* is belonging to family Rosaceae and has many therapeutic activities, including anticancer actions (2). Caffeoylquinic acid is a phenylpropanoid that is a component of all parts of the quince and is able to prevent cancer cell development and promote apoptosis (3). Quince leaves have received increasing attention because they have health-promoting properties (4). Regarding dandelion, the dandelion belonging to the genus *Taraxacum* is a member of the Asteraceae family (5). Dandelion plants contain different phytochemicals that have different biological activities, such as antioxidant, hypoglycemic, immune regulatory and antitumor activities

Key point

Quince and dandelion contain different phytochemicals that show biological activities. Quince and dandelion leaves were extracted with aqueous extraction. They were used to determine their cytotoxicity on Jurkat and K562 cells by flow cytometry *in vitro* killing assay. Concerning the genetic study, the expression level of *BCR ABL* and *TCR* genes were retrieved from gene expression database of normal and tumor tissues 2 (GENT2). Quince and dandelion leaves extract contain substances with potential anticancer cell effect mainly Jurkat cells. BCR ABL and TCR expression level were different in blood cancer patients compared to normal blood samples.

(6). In addition, dandelion influences human cancer cells by encouraging differentiation or controlling cell growth. The methanolic extract of dandelion can reduce the potential of the mitochondrial membrane, which is linked to apoptosis as a mechanism to increase cell death (7). Moreover, dandelion root extract has demonstrated specific effectiveness in enhancing apoptosis in highly aggressive and resistant human chronic myelomonocytic leukemia cell lines (8). The potential cancer activity of transgenic immune cells, such as TCR-NK cells, and other materials, such as plant extracts, was determined via a cytotoxic flow cytometry assay (9).

Jurkat and K562 cells were derived from patients with T-cell leukemia and chronic myeloid leukemia (CML), respectively. Meanwhile, Jurkat cells are T cells that are positive for the T-cell receptor (TCR), which is a complex protein (9). Four TCR genes in the human genome combine to form two different heterodimers; either TCRα/TCRβ or TCRγ/TCRδ (10); since, the bulk of mature T cells exhibit TCRα and TCRβ (11). The TCR is the most extensively studied protein in T cells. Additionally, K562 cells are CML cell lines that express the BCR-ABL fusion gene (12). The fusion gene *BCR-ABL* is a significant biological basis and target for CML. The persistent kinase activity of the oncogenic BCR-ABL fusion protein causes myeloid cells to proliferate uncontrollably through a variety of downstream pathways (13).

Objectives

There are few or no studies on the impacts of quince and dandelion leaf extracts on the Jurkat and K562 cell lines. Therefore, in the current investigation, the cytotoxic potential of quince and dandelion leaf extracts against the Jurkat and K562 cell lines was assessed via flow cytometry cytotoxicity assays. In addition, the expression levels of the *TCR* and *BCR-ABL* genes were targeted for study on the basis of data retrieved from the GENT2 database for Jurkat and K562 cells, respectively.

Materials and Methods

Quince and dandelion leaf aqueous extraction

The current *in vitro* experimental study involved the collection of quince and dandelion leaves which were dried at room temperature for several days. The dried leaves were ground into a powder using blender. Then, 100 mL of distilled water was added to 10 g of each prepared powder, which was mixed with a magnetic stirrer for one hour at room temperature (approximately 25 °C). Afterward, the solutions were placed in a refrigerator at 4 °C overnight (~12 hours). Finally, the solutions were filtered through filter paper and evaporated at 40 °C by using a drier to obtain concentrated extracts.

Preparation of stock extracts

Stock extracts (50 mg/mL) of quince and dandelion leaves were made by dissolving 100 mg of each aqueous extract in 2 mL of 10% DMSO. The solutions were mixed well by using a shaker to dissolve the extracts. Phosphate-buffered saline (PBS) was conducted to make 10% dimethyl sulfoxide (DMSO). After one day, a 0.22 µm filter was used to filter the prepared stock extract solutions. Then, from stock extract solutions, two doses (0.5 and 5 mg/mL) of each extract were examined based on previous study (14).

Leukemia cell lines

Leukemia cell lines (Jurkat and K562) were acquired from the American Type Culture Collection (ATCC). They were grown in RPMI 1640 medium supplemented with 10% (vol/vol) HI FBS. The cells were split every 2–3 days to keep their density and maintained at 37 °C in a humidified 5% CO_2, 95% air incubator.

Flow cytometry-based in vitro killing assay of extracts

The cytotoxicity of filtered quince and dandelion leaf extracts was investigated in Jurkat and K562 cells. Two doses (0.5 and 5 mg/mL) of each extract were examined on 0.1×10^6 cells in a 200 µL total volume per well of a 96-well flat bottom plate for 20 hrs. For the control groups, 2 µL and 20 µL of 10% DMSO were used as the control groups for the 0.5 and 5 mg/mL aqueous extracts used, respectively. After incubation, all the cells were harvested, washed and stained with a LIVE/DEAD™ Fixable Aqua Dead Cell Stain Kit from Thermo Fisher Scientific for flow cytometry via a CytoFLEX S (Beckman Coulter Life Science) device.

Gene expression profile data retrieval

To compare the expression levels of preferred genes (*BCR ABL* and *TCR* genes) in blood cancer patients with those in healthy blood participants, a gene expression database of normal and tumor tissues 2 (GENT2) (http://gent2.appex.kr/gent2/) was applied, which provides gene expression profiles for many samples via two different platforms (Affymetrix U133Plus2 and Affymetrix U133A).

Statistical analysis

The flow cytometry data were analyzed with FlowJo™ version 10.8.1 software. Statistical analysis of the flow cytometry data was subsequently carried out via GraphPad Prism version 9.0. One-way ANOVA with Dunnett's multiple comparisons test was carried out to evaluate the statistically significant differences among the three groups. Moreover, T-test was conducted for comparisons between two groups. Accordingly, *P* value of 0.05 or less was considered statistically significant.

Results

Flow cytometry-based in vitro killing assay of Jurkat cells

The gating strategy used to obtain flow cytometry data from the control groups to assess the cytotoxicity of DMSO

on Jurkat cells is shown in Figures 1A and 1B. The same gating strategy was applied to the other groups. Quince and dandelion leaf extracts were shown to be cytotoxic to Jurkat cells in this study. In particular, 5 mg/mL aqueous extracts of both quince and dandelion leaves significantly increased the killing of Jurkat cells (Figures 2 and 3).

Flow cytometry-based in vitro killing assay of K562 cells

For flow cytometry data analysis via FlowJo, as the same gating strategy as that employed for the control groups was also used to determine the cytotoxicity of DMSO on K562 cells, was applied to the other groups too (Figure 4A and 4B). Compared with the control, the aqueous leaf extracts (0.5 mg/mL) of both plants didn't show statistically significant difference in term of cytotoxicity. However, 5 mg/mL aqueous extracts of both plant leaves significantly increased killed number of K562 cells compared with that in the control groups (Figures 5 and 6).

BCR ABL and TCR expression retrieval from databases

In the current research, the assessment of gene (*BCR, ABL* and *TCR*) expression in the database of GENT2 revealed differences between the control group and patients diagnosed with blood cancer (Table 1). Additionally, *BCR ABL* expression was significantly greater in blood cancer patients than in controls when the U133-plus 2 and U133A platforms were used. However, our research results demonstrated that the average

TCR expression was greater in control patients, however not significantly different from that in blood cancer patients when U133A platforms were conducted. With respect to the use of the U133-plus 2 platform for TCR expression, data were not available.

Discussion

The phytochemical components of quince and dandelion extracts work to kill leukemia cells, this is highlighting their important in traditional medicines. Natural sources of chemicals, such as dandelions, can act as reservoirs of strong bioactive compounds that prevent various cancer types without having any negative side effects (15). Some compounds found in dandelion may be

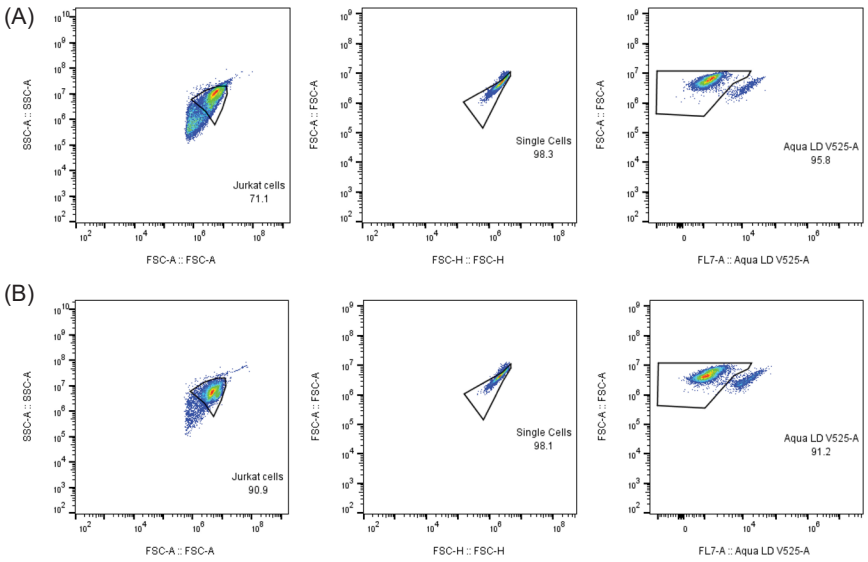

Figure 1. Flow cytometry dot plot gating strategy images of the control groups. Live cells were gated on single cells. Single cells were gated on Jurkat cells. A) Effects of 2 µL of 10% DMSO on Jurkat cells. B) The cytotoxicity of 20 µL of 10% DMSO to Jurkat cells.

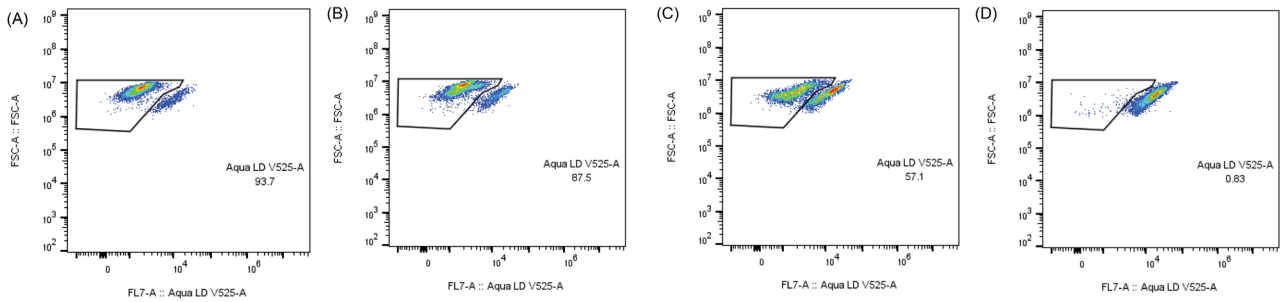

Figure 2. Cytotoxic effects of aqueous extracts of quince and dandelion leaves on Jurkat cells. Dot plot flow cytometry images are presenting only one replication of experiments. A) 0.5 mg/mL of quince. B) 0.5 mg/mL of dandelion. C) 5 mg/mL of quince. D) 5 mg/mL of dandelion.

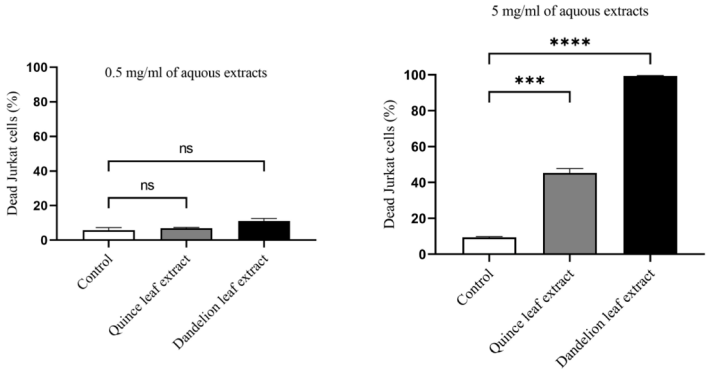

Figure 3. Cytotoxic effects of 0.5 and 5 mg/mL aqueous extracts of quince and dandelion leaves on Jurkat cells. ns; non-significant; *** *P* value <0.001; **** *P* value <0.0001.

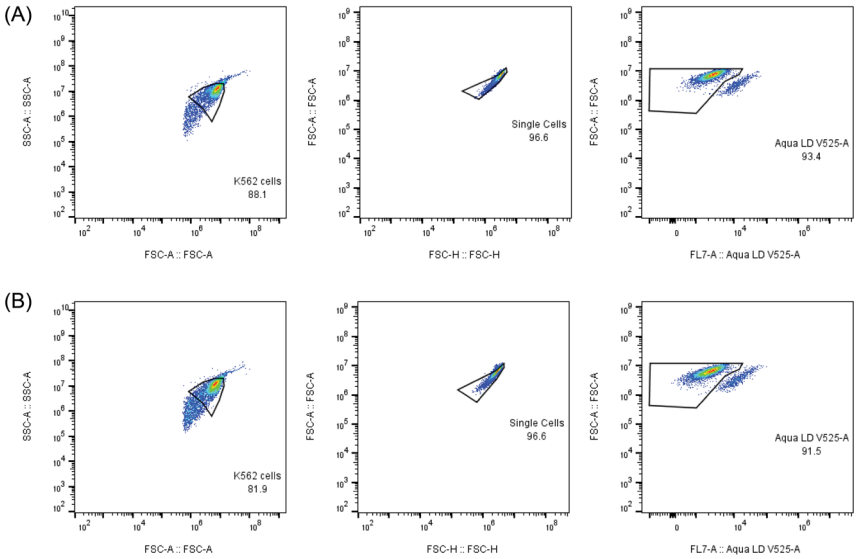

Figure 4. Flow cytometry dot plot gating strategy images of the control groups. Live cells were gated on single cells. Single cells were gated on K562 cells. A) The cytotoxicity of 2 µL of 10% DMSO to K562 cells. B) The cytotoxicity of 20 µL of 10% DMSO to K562 cells.

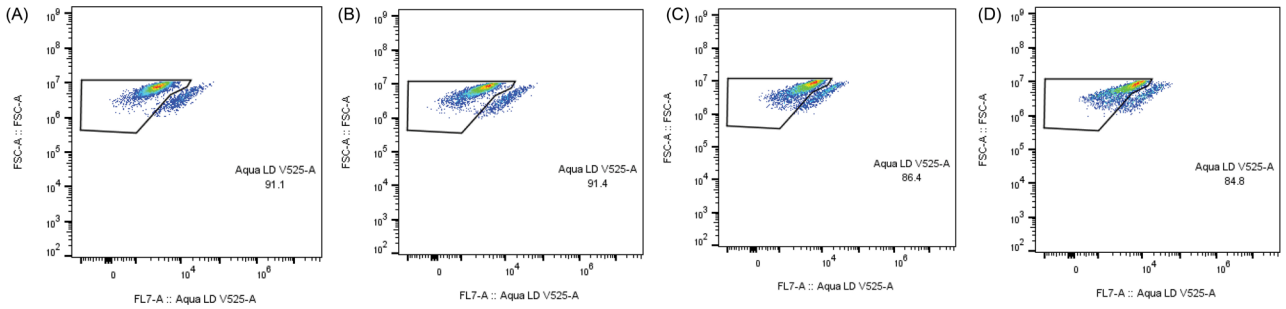

Figure 5. Cytotoxic effects of aqueous extracts of quince and dandelion leaves on K562 cells. Dot plot flow cytometry images are presenting only one replication of experiments. (A) 0.5 mg/mL of quince. (B) 0.5 mg/mL of dandelion. (C) 5 mg/mL of quince. (D) 5 mg/mL of dandelion.

effective in the treatment of cancer (16). Dandelion was found to inhibit cancer cell invasion by decreasing focal adhesion kinase phosphorylation levels and attenuating matrix metalloproteinase activities (17). The fresh water dandelion root extract was effective at stimulating the apoptosis of Jurkat cells (18). In addition, another study reported that dandelion extract stimulates apoptosis in another type of cell line (19). These results are supporting our results in which leaf extracts of dandelion significantly killed more Jurkat cells. Regarding the quince extracts, the aqueous quince extract demonstrated antioxidant ability and cytotoxic activity in human cancer cell lines (20), suggesting that it can be used to inhibit or slow oxidative stress-induced events in malignant cells. Moreover, quince

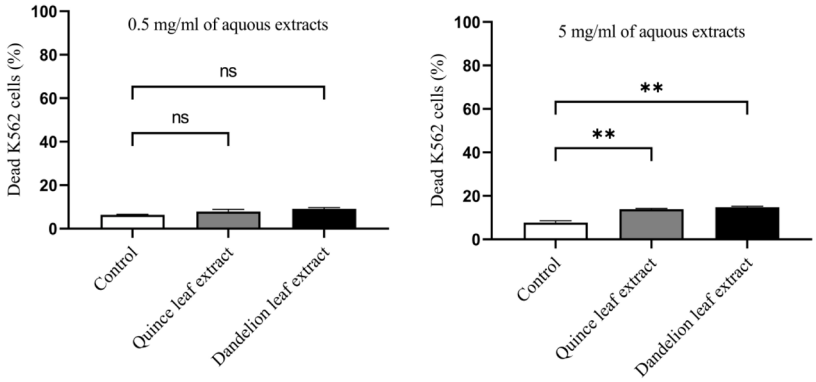

Figure 6. Cytotoxic effects of 0.5 and 5 mg/mL aqueous extracts of quince and dandelion leaves on K562 cells. Ns; non-significant; ** *P* value <0.01.

extracts contain excessive concentrations of triterpenes that reduce the viability of different cancers, including breast, colon, and lung cancer; melanoma; and hepatic carcinoma (21,22). All this anticancer activity of quince and dandelion are due to their phytochemical contents.

In our results, flow cytometry revealed differences in the cytotoxic responses between the two cell lines Jurkat and K562. Jurkat cells showed significant cytotoxicity with both doses of dandelion extract, while K562 cells were more resistant to quince extract. This may indicate that different cancer cell lines have varying sensitivities to phytochemical compounds. Regardless of the chemical used to induce apoptosis, K562 cells appear to be more resistant to it. This resistance can be linked to the unregulated ABL kinase activity of BCR-ABL (23). Our results are in agreement with those of researchers who demonstrated that the extract of pear (the same class of quince plant) can induce apoptotic and cytotoxic effects on K562 cells (24). Other studies reported that successful treatment of leukemia (K562) and prostate cancer (PC-3) cell lines was dandelion extract (25), which is in line with the results of the current research. Currently, more useful databases are available to study genes at different angles, including gene expression. The available GENT2 database was used to study the expression of genes (26). The fusion of the BCR gene to the ABL gene produces the BCR ABL oncogene. The increased ABL tyrosine kinase activity of the BCR ABL fusion protein is essential for the transformation of hematopoietic cells. BCR ABL-transformed CML cells exhibit improved survival, altered adhesion, and decreased growth factor needs and apoptosis (27). Disease progression has been linked to elevated BCR ABL expression levels in CML cells (28). These agree with our flow cytometry cytotoxic assay results in which K562 cells have more resistance to plant leaf extracts compared to Jurkat cells. TCR expression was greater in normal healthy cells than in cancer blood in the present study. T cells normally have TCRs and were recently transformed into natural killer cells to fight cancer cells (9). T cells undergo alterations at the molecular and cellular levels as a result of the interaction of the TCR with an MHC-antigenic peptide combination (29).

Conclusion

An increase in dead Jurkat and K562 cells was observed with both of our leaf extracts (quince and dandelion) compared with untreated cells. These results confirm that aqueous extracts from quince and dandelion leaves contain substances with potential anticancer effects on cells, especially Jurkat cells. Thus, these compounds could be used as supportive anticancer drugs or alternatives to other chemical compounds in the future. In addition, the results identified a valuable source of the anticancer effects of aqueous dandelion extracts from leaves at doses of both 0.5 and 5 mg/mL that can be dependent upon the treatment of cancer, including acute lymphoblastic leukemia and CML. Moreover, the BCR ABL expression level was greater in patients with blood cancer, which is the main cause of leukemia, especially CML. However, TCR expression was lower in blood samples from patients with cancer than in normal blood samples, which is related to the down-regulation of TCRs that occurs in patients with cancer.

Table 1. Illustrates the gene expression profile of *BCR, ABL* and *TCR* genes in blood

Blood	Significant gene expression (Two sample T test)							
	GPL570 platform (HG-U133_Plus_2)				GPL96 platform (HG-U133A)			
	P value	Log2FC	Average expression level (1097 Normal blood samples)	Average expression level (13193 Blood cancer samples)	*P* value	Log2FC	Average expression level (915 normal blood samples)	Average expression level (2083 Blood cancer samples)
BCR ABL	<0.001	0.231	9.7201347	9.9085816	<0.001	1.423	6.9906626	8.4129608
TCR	-	-	-	-	0.121	-0.098	5.9611205	5.163352

Study Highlights

What is the current knowledge?

- Quince leave has received increasing attention because it has health-promoting properties.
- Dandelion contains different phytochemicals that show biological activities.

What is new here?

- Quince and dandelion leaf extracts contain substances with potential anticancer effects, mainly on Jurkat cells.

Limitations of the study

A limitation of the current research was the lack of determination the anticancer activity of different parts of quince and dandelion, which is essential for identifying which specific parts of these plants may have anticancer potential.

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Authors' contribution

Conceptualization: Azheen Subhi Abdulrahman and Khder Hussein Rasul.
Data curation: All authors.
Formal analysis: Khder Hussein Rasul.
Funding acquisition: All authors.
Investigation: Azheen Subhi Abdulrahman and Shang Ziyad Abdulqadir.
Methodology: Azheen Subhi Abdulrahman and Khder Hussein Rasul.
Project administration: All authors.
Resources: Khder Hussein Rasul, Inaam Ahmad Mustafa and Shang Ziyad Abdulqadir.
Software: Khder Hussein Rasul.
Supervision: Khder Hussein Rasul.
Validation: Inaam Ahmad Mustafa and Shang Ziyad Abdulqadir.
Visualization: Inaam Ahmad Mustafa and Shang Ziyad Abdulqadir.
Writing–original draft: Azheen Subhi Abdulrahman and Khder Hussein Rasul.
Writing–review & editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The scientific committee at the College of Science, Salahaddin University Erbil (Iraq) approved the current study (No. 4C/206). This study is conducted on cell line as an *in vitro* experimental investigation and performed in accordance with the principles of. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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