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THE EFFECT OF DANDELION HYDRO-ALCOHOLIC EXTRACT AND ITS ACTIVE CONSTITUENT ON RADIOSENSITIVITY OF GLIOBLASTOMA CANCER CELLS: AN *IN VITRO* STUDY

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Abstract – *Objective:* *Radiation therapy is one of the many methods that are used to cure cancers. Considering the high resistance of cancer cells to radiation therapy and its many side effects, and considering that in recent years the high medicinal potential of plants has been noticed, the aim of this study is to investigate the effects of the dandelion hydro-alcoholic extract and its active constituent on the radiation therapy cytotoxic effect in glioblastoma cancer cells.*

Materials and Methods: *After treatment with extract and taraxasterol, the cell viability was evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide assay. Then the effect of the combination of extract and taroxasterol with ionizing radiation was tested. The apoptosis cell death was investigated by diphenylamine assay and real-time technic.*

Results: *After treatment with extract and taraxasterol, cell viability was decreased in a dose-dependent manner. The extract and taraxasterol increased the sensitivity of cells to ionizing radiation. In addition, after treatment with the extract and taraxasterol, the amount of apoptosis induced by ionizing radiation in the cells increased. After treatment with extract, taraxasterol and ionizing radiation, the expression of Bax and p53 increased and the expression of Bcl-2 decreased.*

Conclusions: *Using the dandelion along with radiation therapy may show a better response to treatment in glioblastoma patients.*

KEYWORDS: *Dandelion, Taraxasterol, Glioblastoma multiforme, Radiation therapy.*

INTRODUCTION

Cancer is the main cause of death in developed countries and the second cause in developing countries[1]. Brain tumors are the second and third most common types of cancer in children and adults, respectively[2]. Glioma is the most common type of central nervous system tumor[3]. Grade IV glioma, which is called glioblastoma multiforme (GBM), is the most malignant and progressive primary brain tumor, which is one of the deadliest solid human tumors[4]. The average life of treated patients is only 12 to 15 months and only 3-5% of patients survive for more than 3 years[5]. The standard treatment of this disease includes surgery and removing the tumor as much as possible, followed by radiation therapy and chemotherapy[6]. Despite these aggressive treatments, the survival rate increases in just a few months, because the tumor has different ways of developing resistance to chemotherapy and radiation, either activating the DNA repair system or making changes in the cell cycle and regulation of apoptosis. However, little is known about the mechanisms involved in

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radiation therapy resistance in GBM, and the underlying mechanism of its acquisition is unclear[7].

Some plants have anti-cancer agents, whose derivatives have been proven to be used for the treatment or prevention of cancer in humans. Plants of the genus Taraxacum of the family Asteraceae or Compositae has a very valuable historical background, which demonstrates their wide range of medicinal potential. Dandelion is a perennial weed. The well-known medicinal effects, along with low toxicity, make this plant a suitable food source. Dandelion flowers, leaves, and roots, apart from being used as a medicinal agent, are turned into various food products. Due to its history as a medicinal plant, it is often marketed as a healthy food. The use of dandelion fresh salad has been suggested by the Food and Agriculture Organization to improve the nutritional status of population areas with poor economic resources. In the traditional medicine system, all parts of dandelion, especially the roots, have laxative, cholagogue, purifying, diuretic, liver strengthening, appetizing and tonic properties[8]. Taraxasterol (3β, 18α, 18α)-Urs-20(30)-en-3-ol) is a pentacyclic triterpene and has been isolated from various plants including dandelion.

As mentioned before, patients with GBM have a relatively short life span after being diagnosed and having symptoms, removing the tumor, and undergoing chemotherapy and radiation therapy due to the very low sensitivity of tumor cells to treatment. Increasing the dose of medicine and radiation therapy to increase the effect causes very severe side effects. Considering the necessity of identifying new treatment methods and strengthening the effectiveness of common treatments, this research aimed to investigate the effect of dandelion hydro-alcoholic extract and its active constituent on GBM cell line.

MATERIALS AND METHODS

Preparation of dandelion extract

The dandelion plant was collected from the lands around Kermanshah in the west of Iran and its impurities were separated. After confirmation by the botanist, the plant materials were dried in the shade for 5 days and ground into powder form; after that, 100 g of plant powder was added to 70% ethanol (ratio 1 to 4). The resulting solution was kept in a warm water bath at 35°C for 48 h in the dark. In the next step, the solution was gradually poured on Buchner filter paper and filtered with the help of a vacuum pump. Then, it was transferred to the rotary device to collect the excess solvent and concentrate. The process of separation continued until a thick extract was obtained. The extract was dried at room temperature and turned into powder. The obtained extract was dissolved in the culture medium and after filtering it was used to treat the cells[9].

Cell culture

The GBM cell line (T98G) (Pasteur Institute, Tehran, Iran) was prepared and cultured in Dulbecco's Modified Eagle's Medium (Gibco Company, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (Gibco Company, Grand Island, NY, USA) and 1% penicillin/streptomycin antibiotic solution (Gibco Company, Grand Island, NY, USA) at 37°C, 5% carbon dioxide and 95% humidity. The cells of the fourth passage are selected for the next steps.

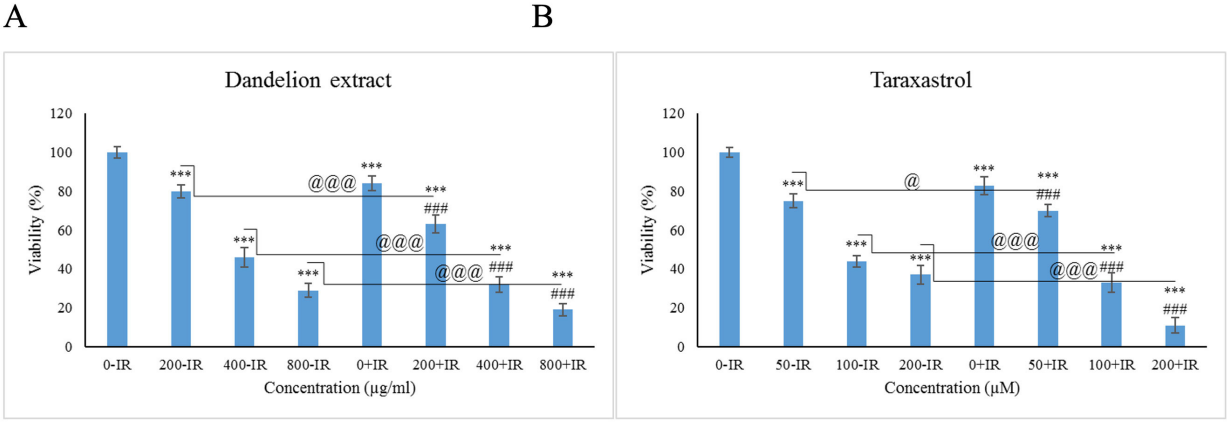

Fig. 1. The effect of (A) dandelion extract and (B) taraxasterol and/or ionizing radiation on the viability of glioblastoma cells. Cell viability was evaluated by MTT test. The control group received drug-free medium. *** indicates $p<0.001$ compared to control, ### indicates $p<0.001$ compared to irradiated control cells and @ indicates $p<0.05$ and @@@ indicates $p<0.001$ compared to the same concentrations of extract or taraxasterol without radiation.

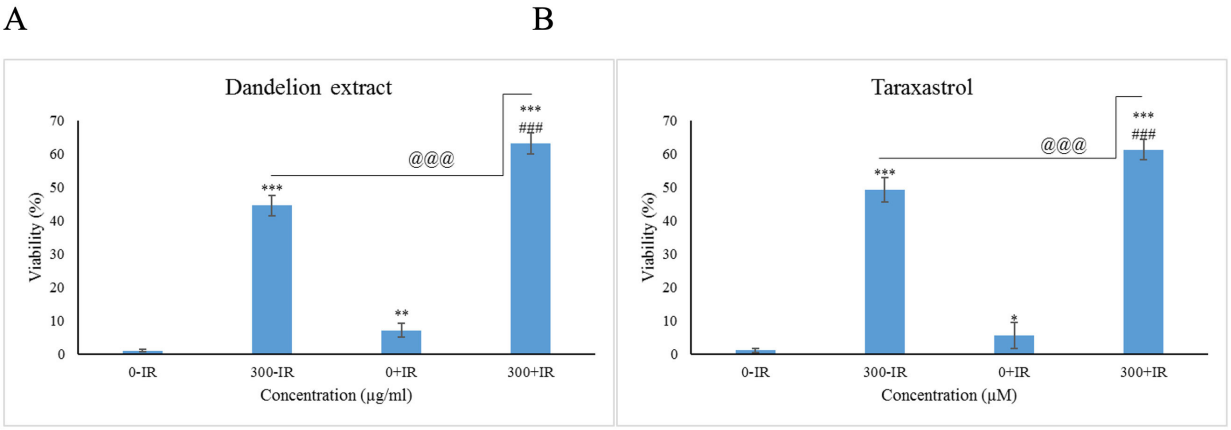

Fig. 2. The effect of (A) dandelion extract and (B) taraxasterol and/or ionizing radiation on apoptosis of glioblastoma cells. Apoptosis was evaluated by diphenylamine assay. The control group received drug-free medium. *** indicates $p<0.001$ compared to control, ### indicates $p<0.001$ compared to irradiated control cells and @@@ indicates $p<0.001$ compared to the same concentrations of extract or taraxasterol without radiation.

Radiation and treatment of cells

Irradiation with a dose of 4 Gy was performed using a 6 MV X-ray beam from a medical linear accelerator with a field size of 25 x 25 cm^2 and a source-cell distance of 100 cm at a 180° gated angle. Also, treatment with concentrations of 200, 400, and 800 µg/ml of dandelion plant extract and with concentrations of 50, 100, and 200 µM of taraxasterol was performed for 24 hr with and without radiation.

Viability assay

The cells were seeded in 96-well plates (15×103 cells/well) and incubated until the density reached 80%. Then, they were treated with extract and taraxasterol, and after an hour, the cells were exposed to radiation. Then it was incubated for 24 hr and 10 µl of 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide solution (Sigma-Aldrich, St. Louis, MO, USA) was added to each well and incubated for 3 hr in the dark at 37°C. Then, 100 µl dimethyl sulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) was added to each well and the absorbance of samples was read at 570 nm using an ELISA reader. The percentage of cell viability was calculated from the following equation:

Cell viability (%) = (Abs test cells/Abs control cells) × 100

Apoptosis assay

The percentage of DNA fragmentation cells before and after treatment was determined by diphenylamine assay. 5 × 10^6 cells were resuspended in 1 mL of Tris-TAPS-Ethylene diamine tetra acetic acid (TTE) buffer (Sigma-Aldrich, St. Louis, MO, USA) and centrifuged at 20,000 g for 10 min at 4°C. Then

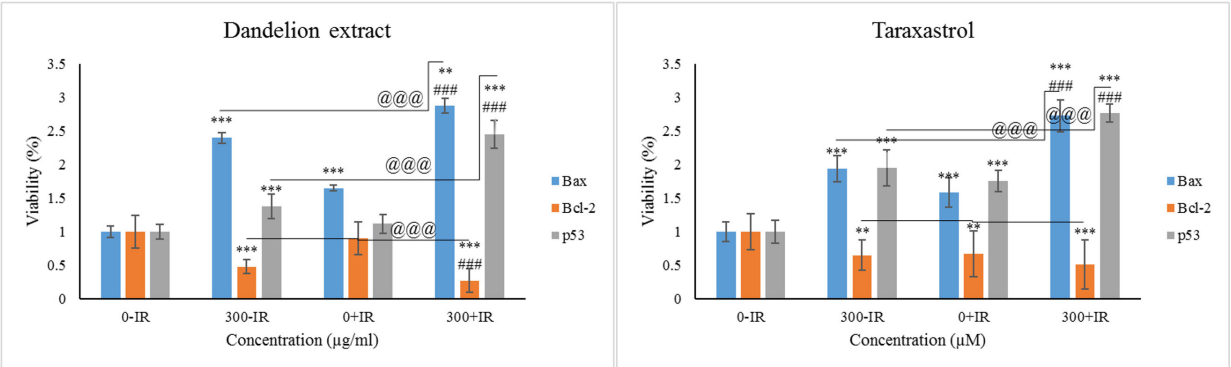

Fig. 3. The effect of (A) dandelion extract and (B) taraxasterol and/or ionizing radiation on Bax, Bcl-2, and p53 genes expression in glioblastoma cells. Gene expression was evaluated by Real-time PCR assay. The control group received drug-free medium. ** indicates $p<0.01$ and *** indicates $p<0.001$ compared to control, ### indicates $p<0.001$ compared to irradiated control cells and @@@ indicates $p<0.001$ compared to the same concentrations of extract or taraxasterol without radiation.

the intact chromatin (pellet) was separated from the damaged DNA (supernatant). Supernatants were transferred to new tubes (sample A) and pellets were resuspended in 1 mL of TTE buffer plus 1 mL of 25% trichloroacetic acid (Sigma-Aldrich, St. Louis, MO, USA) and incubated overnight at 4°C. Then the samples were centrifuged again. To cleave DNA, 160 mL of 5% trichloroacetic acid was added to each pellet. Samples were heated for 15 min at 90°C, then 320 µL of freshly prepared diphenylamine solution (Sigma-Aldrich, St. Louis, MO, USA) was added to each sample and incubated for 4 hr at 37°C (sample B). Finally, the absorbance of samples A and B was measured at 600 nm using a spectrophotometer. The percentage of fragmented DNA was calculated using the following formula:

Percentage of DNA fragmentation = [OD660 (A) /OD660 (B) − OD660 (A)] × 100

Gene expression analysis

The Bax, Bcl-2 and p53 mRNA expression before and after treatment were analyzed by real-time PCR. Total RNA from cells was extracted by a total RNA isolation kit (DENAzist, Tehran, Iran), and the complementary DNA (cDNA) synthesis was carried out a using cDNA synthesis kit (Vivantis Technologies, Selangor DE, Malaysia). Real-time PCR was performed using SYBR Premix Ex Taq technology (TaKaRa Bio Inc, Otsu, Shiga, Japan) on the Applied Biosystems StepOne Real-Time PCR System. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) served as an internal control, and fold change in the relative expression of each target mRNA was calculated based on the comparative Ct (2ΔΔct) method. The primer sequences are as follows:

Bax:
Forward: 5-CCTGTGCACCAAGGTGCCGGAACT-3
Reverse: 5-CCACCCTGGTCTTGGATCCAGCCC-3
Bcl-2:
Forward: 5-TTGTGGCCTTCTTTGAGTTCGGTG-3
Reverse: 5-GGTGCCGGTTCAGGTACTCAGTCA-3
P53:
Forward: 5-TAACAGTTCCTGCATGGGCGGC-3
Reverse: 5-AGGACAGGCACAAACACGCACC-3
GAPDH:
Forward: 5-TCCCTGAGCTGAACGGGAAG-3
Reverse: 5-GGAGGAGTGGGTGTCGCTGT-3

Statistical analysis

All experiments were performed in triplicate and repeated independently at least three times and data were expressed as means ± standard deviation (SD). Comparisons between groups were performed by Tukey's test, one-way analysis of variance and differences were considered significant when $p<0.05$.

RESULTS

The effect of dandelion extract and/or ionizing radiation on cell viability

After 24 hr, dandelion extract caused a significant decrease in cell viability ($p<0.05$). Also, ionizing radiation caused a significant decrease of 16% in cell viability ($p<0.05$). Comparing cell viability between groups treated with the same concentrations of the extract with and without receiving ionizing radiation showed that the viability was significantly lower in groups receiving radiation ($p<0.05$). Also, the comparison of cell viability in groups receiving radiation showed that treatment with the extract significantly increases the sensitivity of cells to radiation ($p<0.05$).

The effect of taraxasterol and/or ionizing radiation on cell viability

After 24 hr, taraxasterol caused a significant decrease in cell viability ($p<0.05$). Also, ionizing radiation caused a significant decrease of 17% in cell viability ($p<0.05$). Comparing cell viability between groups treated with the same concentrations of the extract with and without receiving ionizing radiation showed that the viability was significantly lower in groups receiving radiation ($p<0.05$). Also, the comparison of cell viability in groups receiving radiation showed that treatment with the extract significantly increased the sensitivity of cells to radiation ($p<0.05$).

The effect of dandelion extract and/or ionizing radiation on cell apoptosis

After 24 hr, dandelion extract caused a significant increase in cell apoptosis ($p<0.05$). Also, ionizing radiation caused a seven-fold significant increase in cell apoptosis ($p<0.05$). Comparison of apoptosis between groups treated with the same concentrations of extracts with and without receiving ionizing radiation showed that apoptosis was significantly higher in groups receiving radiation ($p<0.05$). Also, the comparison of cell apoptosis in the radiation receiving groups showed that treatment with the extract significantly increased cell apoptosis ($p<0.05$).

ìThe effect of taraxasterol and/or ionizing radiation on cell apoptosis

After 24 hr, taraxasterol caused a significant increase in cell apoptosis (p<0.05). Also, ionizing radiation caused a significant six-fold increase in cell apoptosis (p<0.05). Comparison of apoptosis between groups treated with the same concentrations of taraxasterol with and without receiving ionizing radiation showed that apoptosis was significantly higher in groups receiving radiation (p<0.05). Also, the comparison of cell apoptosis in the radiation receiving groups showed that treatment with taroxasterol significantly increased cell apoptosis (p<0.05).

The effect of dandelion extract and/or ionizing radiation on the expression of the apoptosis-related genes

Molecular investigations showed that treatment with the IC50 concentration of dandelion extract for 24 hr caused a significant increase in Bax and p53 gene expression (p<0.05). Also, this treatment caused a significant decrease in Bcl-2 gene expression in GBM cells (p<0.05). Comparing the expression of these genes in the groups not treated with the extract with and without receiving radiation showed that the only significant change was the increase in Bax gene expression after receiving radiation (p<0.05). The comparison between these three genes in the groups treated with the IC50 concentration of the extract with and without radiation showed that the expression of Bax and p53 in the group under radiation increased significantly compared to the group without radiation, and the expression of Bcl-2 decreased significantly (p<0.05). Comparison between two groups receiving radiation with and without extract treatment showed that extract treatment caused a significant increase in Bax and p53 gene expression (p<0.05). Also, this treatment caused a significant decrease in Bcl-2 gene expression in GBM cells under radiation (p<0.05).

The effect of taraxasterol and/or ionizing radiation on the expression of the apoptosis-related genes

Molecular studies showed that treatment with the IC50 concentration of taraxasterol for 24 hr caused a significant increase in Bax and p53 gene expression (p<0.05). Also, this treatment caused a significant decrease in Bcl-2 gene expression in GBM cells (p<0.05). Comparing the expression of these genes in the groups untreated with the extract with and without radiation showed that there was a significant increase in Bax and p53 gene expression and a significant decrease in Bcl-2 gene expression after radiation (p<0.05). Comparison between the groups treated with the extract with and without radiation showed that the increase in the expression of Bax and p53 was significant in the treated groups, but the decrease in the expression of Bcl-2 was not significant (p<0.05). The comparison between these three genes' expression in the groups treated with the extract with and without radiation showed that the expression of Bax and p53 in the group under radiation increased significantly compared to the group without radiation, but the changes in the expression of Bcl-2 were not significant (p< 0.05).

DISCUSSION

Radiotherapy for GBM is largely ineffective at clinically safe doses, therefore, the study of radiosensitizers is of great importance[10]. In this project, first, the effect of dandelion hydro-alcoholic extract, taraxasterol (its active constituent), and ionizing radiation on the viability of cells was investigated separately. The results showed that after treatment with the extract, taraxasterol, and also after exposing the cells to ionizing radiation, the viability of the cells decreased. In the next step, the IC50 value of dandelion extract and taraxasterol was calculated.

As mentioned in the introduction, despite the recent advances in cancer treatment, there is still no improvement in the life span and quality of life of GBM patients, and the main cause of this problem is resistance to chemotherapy and radiotherapy. Therefore, it is necessary to develop new strategies to overcome this problem. Recently, the use of combination treatments is the most widely used treatment method for deadly diseases such as cancer and AIDS. The main goal of this strategy is to achieve a synergistic therapeutic effect, reduce the dosage and toxicity, and minimize or delay the development of resistance[11].

The results obtained in the simultaneous treatment of T98G cells with extract and radiation or taraxasterol and radiation showed that the combination of the two factors had a more toxic effect than either agent alone.

Today, the use of combination therapy is widely used in the treatment of all types of cancers. Previous studies have shown that combination of temozolomide (the standard chemotherapy drug for GBM with other anti-cancer agents) increased its activity in improving GBM disease. For example, clinical studies have shown that adding

chloroquine to standard GBM treatment had beneficial results[12]. Also, the combination of temozolomide with carmustine as a new adjuvant treatment in GBM patients showed satisfactory effects with tolerable toxicity[13]. *In vitro* studies have also shown that the anti-cancer effect of temozolomide increased in combination with some natural anti-cancer agents[14]. But clinical studies on the effectiveness of these combined treatments have not been done so far.

In the field of increasing sensitivity to chemotherapy, the effects of hydroalcoholic extract of Zataria multiflora on cell death caused by ionizing radiation in GBM cell line (A172) and non-malignant human fibroblasts (HFFF2) have been investigated *in vitro*. A172 and HFFF2 cells were treated with hydroalcoholic extract of dry aerial parts of Zataria multiflora at different concentrations (25, 50, 100, 150, and 200 µg/ml) and then exposed to ionizing radiation. These data demonstrated the radiosensitizing effects of the extract in A172 cells, apparently due to increased radiation-induced apoptosis[15]. Also, the radiosensitizing effects of the extract of Cranberry in GBM cell line (U87) was tested. Cranberry extract alone has little effect on U87 cell survival. However, radiotherapy supplemented with the extract significantly inhibited the proliferation and induced apoptosis of U87 cells compared to radiotherapy alone. The proliferative inhibitory effect of these two agents may be attributed to the up-regulation of p21, along with the downregulation of cyclin B and cyclin-dependent kinase 4[10].

Radiotherapy plays a key role in the local treatment of solid tumors by inducing DNA damage, cell cycle stimulation, and apoptosis. The therapeutic effect of radiotherapy in cancer patients depends on the radiation sensitivity of the tumor and the tolerance of normal tissues[16]. According to the results of our study, dandelion extract showed an effect of increasing radiation sensitivity on GBM cells. Our results are consistent with the results of others who showed that dandelion plant had an anti-neoplasmic effect against cancer cells[8].

In this study, radiation-induced apoptosis in GBM cells was significantly increased following treatment with the extract and taraxasterol. One of the main causes of tumor formation is a defect in the processes of apoptosis, which causes the production of immortal clones of cells. Most chemotherapy drugs as well as the use of radiotherapy increase apoptosis in tumor cells. Failure to induce apoptosis is one of the main causes of drug resistance in cancer[17].

Also, in this project, the expression change of p53, Bax, and 2-Bcl genes was evaluated. The involvement of p53 in apoptotic cell death is mainly in the mitochondrial pathway, but evidence also shows that it can activate the external pathway as well. In addition, evidence also suggests that the key role of this protein in apoptosis is based on its transcriptional regulatory activity. This protein is capable of activating many pro-apoptotic genes, including Bcl-2 family members, such as Bax, NOXA and Puma. Also, p53 can initiate apoptosis by suppressing anti-apoptotic genes such as Bcl-2[18].

In mitochondria, p53 induces the oligomerization of Bax and Bak and physically reacts with Bcl-2 and Bcl-Xl, neutralizing their anti-apoptotic activity and also forming a complex with cyclophilin D, which ultimately leads to the collapse of mitochondrial structure[19].

Many proteins with anti-apoptotic and pro-apoptotic activity have been reported in the cell. The ratio between these proteins plays an important role in regulating cell death. The Bcl-2 family of proteins consists of anti-apoptotic and pro-apoptotic proteins, which play an important role in regulating apoptosis, especially from its internal pathway, because it is at the top of irreversible cell damage. The mentioned proteins mainly act at the mitochondrial level. All members of the Bcl-2 family are located in the outer membrane of mitochondria, where they dimerize and are responsible for membrane permeability by forming ion channels or by creating barriers in the membrane. Bcl-2 is the first known protein of this family, which is encoded by the BCL-2 gene located on chromosome 18q21, which inhibits apoptosis without affecting cell proliferation. Bax protein is a member of the Bcl-2 family and promotes apoptosis. Bax/Bcl-2 ratio determines the occurrence of apoptosis in the cell. In many human cancers, the expression of Bcl-2 is increased, while the expression of Bax is decreased. This factor causes the resistance of most cancer cells to stimuli such as chemotherapy drugs[20].

The results obtained from our investigations showed that after treatment with dandelion extract and/or ionizing radiation, as well as taroxasterol and/or ionizing radiation, the expression of Bcl-2 decreased, and the expression of p53 and Bax increased. Therefore, the expression ratio of pro-apoptotic to anti-apoptotic proteins had changed in the direction of apoptosis.

CONCLUSIONS

In this research, the effect of dandelion extract and/or ionizing radiation, as well as taraxasterol and/or ionizing radiation on T98G cells, was studied separately and simultaneously. The results showed that dandelion plant extract, as well as its active constituent, increased the sensitivity

of GBM cells to radiation therapy. This effect is probably through the increase of apoptosis induced by radiation through the increase of the Bax/Bcl-2 ratio. More *in vivo* and clinical studies are recommended in this field.

Author's Contributions:

S.R-Z.; Designed experiments and supervised the research. S.K-B.; Analysed data and wrote the manuscript. I.R.; Performed the cell culture experiments and done gene expression. All authors read and approved the final manuscript.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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