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Determination of the anticancer effects of M (Mn, Ni, B) doped ZnO nanoparticles against ovarian and breast cancer cells

Derya Yetkin [*1], Saadet Yıldırımcan[2,3], Selma Erat[1,3], Furkan Ayaz[4,5]

[1]Mersin University, Advanced Technology Education Research and Application Center, Türkiye, deryayetkin@mersin.edu.tr, selma.erat@mersin.edu.tr
[2]Mersin University Department of Nanotechnology and Advanced Materials, Türkiye, syildirimcan@mersin.edu.tr
[3]Mersin University, Vocational School of Technical Sciences/Opticianry, Türkiye, syildirimcan@mersin.edu.tr, selma.erat@mersin.edu.tr
[4]Mersin University, Science Institute, Faculty of Arts and Science, Department of Biotechnology, Türkiye, furkanayaz@mersin.edu.tr
[5]Mersin University Biotechnology Research and Application Center, Türkiye, furkanayaz@mersin.edu.tr

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Abstract

Breast cancer has the second highest worldwide incidence rate and it has the highest prevalence among the women. Breast cancer, with its high prevalence rates, affects the lives, living standards, and economies of many patients and their families as well as the healthcare services in the public health institutions. The treatment options of the breast cancer depend on the stage of the cancer. Currently, endocrine therapy, radiotherapy, chemotherapy as well as surgery are among the treatment options. Although chemotherapy is widely used against breast cancer, it also brings detrimental side effects alongside to the patients. Therefore, it is imperative and urgent to develop novel therapeutic options against breast cancer. In order to overcome the side effects related with the chemotherapy application, nanomedicine-based agents have gathered an immense attention due to their; enhanced targeting properties, better bioavailability, biocompatibility and multiple functions. ZnO nanoparticles have been in use in cosmetics, dye production and surface modifications of the industrial products. It has also been used in biological and biomedical fields in the recent years. In the light of these, we aimed to find out the possible effects of the anti-proliferative effects of pure, Mn, B and Ni doped ZnO nanoparticles in our project proposal. A 2780 ovarian cancer cell line, ER+ breast cancer cell line (MCF7), ER- breast cancer cell line (MDA-MB-231), and human fibroblast cell line (BJ-5TA). In this way, the appropriate concentration of the most effective nanoparticle type to be used in different cancer types was determined for future experiments on breast cancer and ovarian cancer. In addition, with this study, a preliminary study was obtained in order to see in which cancer type the new drug candidates are more effective, and this study is a preliminary study for further studies of possible drug candidates.

Introduction

Breast cancer poses a serious threat to public health with its highest prevalence rate among women. 25% of cancers seen in women are diagnosed as breast cancer. In terms of being fatal, breast cancer ranks 5th when compared to other cancer types in women. Ovarian cancer comes right after breast cancer. A definite solution has not been produced yet against these two cancer types, which are numerically high in terms of both mortality rate

and incidence [1]. With the side effects of radiotherapy and chemotherapy, they significantly reduce the living standards of the patients. There is a serious need for new generation drug candidates, especially in the field of chemotherapy [2]. Nanoscience and nanotechnology, nanomaterials, have attracted great attention in the last decade due to their unique and superior physical/chemical characteristics and have been utilized in a wide range of applications [3]. Zinc oxide (ZnO) has a relatively wider bandgap (3.37 eV) as a semi-conductor [4] with properties suitable for wide applications such as cancer medicine, bioimaging, and drug delivery. (60 meV). When doped with various transition metals such as ZnO, Fe, Mn, it exhibits different behavior in electrical, magnetic and optical excitation properties [5]. ZnO nanoparticles are not biologically inert and cause cytotoxicity, apoptosis, cell cycle alteration, and DNA damage [4]. Nanobiotechnology has been shown to have the potential to offer a more targeted approach to treating cancer patients. At the nanoscale, materials can have new and more advanced physico chemical properties that are not found in micron or larger sized particles composed of the same material systems. With these characteristics, they have the potential to lead to unique biological and medical applications [6].

Material and Method

Cell Viability Test

Cancer cells cultured by MTT method can be detected colorimetrically and quantitatively. This method is based on the principle that the MTT dye of intact mitochondria can cleave the tetrazolium ring. MTT is a water-insoluble formazan reduced substance and appears in color by a mitochondria-dependent reaction. The MTT reduction property of cells is calculated according to the correlation of the dye density obtained as a measure of cell viability with the number of viable cells. Cell viability will be evaluated using the Vybrant® MTT Cell Proliferation Assay (Invitrogen Corporation, CA, USA). In the study, treated with ZNO at different concentrations (1 µg/ml, 50 µg/ml, 100µg/ml). Effects on proliferation of A 2780-CP, ER + breast cancer cell, ER - breast cancer cell, human fibroblast cell lines by MTT cell proliferation method researched. After the cells were plated, they were incubated at 37 °C for 24 hours and 1 night in a 5% carbon dioxide incubator. Compounds were then added to each well and after 72 hours MTT was added to each well to incubate the samples for 4 hours. Absorbance measurements were then made at 570 nm with a spectrophotometer. IC50 values were calculated using the SPSS program (SPSS. Inc, Chicago).

Results

The data have been doped with different metals after exposure to ZnO and after the cell proliferation index value, after 72 hours of treatment (all comparisons $p>0.05$) were decreased in a time dependent manner in comparison with the control group and after IC50. The value of ZNO derivatives was calculated. It was found that there was a time-dependent decline in the proliferation of cancer cells 72 hours after administration of ZNO and its derivatives in ER- and ER+ breast cancer cells compared to the control group (all comparisons $p<0.05$). A time-dependent decrease in cell proliferation was observed in ovarian cancer cells 72 hours after administration (all comparisons were $p<0.05$), but the IC 50 value was higher in the A2780-CIS cancer cell line than in SKOV cells.

Discussion

Breast and ovarian cancer are the most common cancer types among women globally and in our country. Although it is aimed to be treated with chemotherapy, radiotherapy and surgical interventions, the frequency of relapse in patients and especially the side effects that occur after chemotherapy or radiotherapy emphasize the necessity of developing new generation drug candidates in this area. Preliminary study data of nanoparticles used in this project are important in terms of presenting an alternative to the deficiencies in this regard In previous studies, ZnO, one of many nanoparticles; It has been shown that it increases oxidative stress in cancer cells by causing an increase in reactive oxygen radicals (ROS), and ultimately causes cytotoxicity, apoptosis, cell cycle changes and DNA damage in cancer cells [4,6,7].

Previous studies have shown that ZnO nanoparticles increase oxidative stress and intracellular Ca+2 levels and decrease mitochondrial membrane potential (MPT) in different cancer cell lines. It has been reported that ZnO nanoparticles stimulate interleukin (IL-8) expression and reduce mitochondrial membrane potential (MPT) in BEAS-2B bronchial epithelial cells and A549 alveolar adenocarcinoma cells [8]. It has also been shown that these nanoparticles activate the p53 pathway in RAW264.7 cells [9,10]. It has also been reported that metal nanoparticles stimulate the expression of Bcl-2, a pro-apoptotic protein, in human breast cancer, PC12, and fibroblast cells, activate the PARP and caspase cascades, and induce apoptosis by causing mitochondria and DNA damage [11-13]. Ghaemi et al. conducted a study on preventing organelle damage and stopping the cell cycle progression of the melanoma cells by altering the intracellular ROS level of Ag: ZnO nanoparticles. According to

this study, in the process of photodynamic therapy, it was concluded that the production of ROS by Ag: ZNO nanoparticles under UV light can disturb the homeostasis of melanoma, while it did not affect the fibroblasts [14]. In studies conducted in ovarian cancer, it has been shown that ZnO nanoparticles do not damage fibroblast cells when triggering apoptosis in cancer cells (38). In this study, we aimed to determine the in-vitro efficacy levels of ZnO nanoparticles doped with different metals that have not been studied before against breast and over cancer. In this study, we have shown that ZNOs doped with different metals cause a decrease in the proliferation of breast and ovarian cancer cells depending on concentration and time, and these findings support previous studies. However, further studies are needed to compare these ZNOs doped with different metals with drugs used in routine cancer treatment, and through which pathways these ZNOs affect cancer cells.

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