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RESEARCH ARTICLE

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The valuable effects of Anzer bee products against the gliclazide-induced damage on human cell viability

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ABSTRACT: The studies on the benefits of natural products are still up to date around the world. The drugs are powerful agents for the treatment of the diseases, but the long-term use of the drugs may develop clinically unnoticeable side effects. They can cause damage at the cellular level and the cell viability can be affected. This status can lead to the development of some new diseases or cancer which is the most feared. We investigated the harmful effects of a frequently used antidiabetic drug gliclazide, on Healthy Human Pancreatic Cell "hTERT-HPNE" and aimed to improve these harmful effects with the special natural products of Anzer Plateau bees in Eastern Black Sea Region of Turkey. The cytotoxic and genotoxic effects of the drug gliclazide were investigated using different tests such as MTT, Flow Cytometry-Apoptosis. Anzer honey, pollen and propolis were analyzed by G/C-MS. The decrease in cell viability at all concentrations of the drug gliclazide was statistically significant compared to the negative control ($p<0.05$). A statistically significant decrease in gliclazide-induced apoptosis was detected with the addition of Anzer honey, pollen and propolis to hTERT-HPNE cells ($p<0.05$). Anzer honey, pollen and propolis maintained cell viability and healed the damage caused by the drug, This study may contribute to other studies testing the healing properties of natural products at cellular level.

KEYWORDS: Cell viability, Drug, hTERT-HPNE, Anzer honey, Apoptosis

INTRODUCTION

Diabetes Mellitus Type 2 (T2DM) is a chronic endocrine-metabolic disease due to insulin deficiency or ineffectiveness and it is seen at a high rate in the people, with an increase in morbidity and mortality. This rate is predicted to reach 25% in 2030 according to the data of International Diabetes Federation [1]. The T2DM theraphy is based on keeping plasma glucose at normal levels with adjusting lifestyle, exercise and medication. During the use of oral antidiabetics; treatment satisfaction, quality of life, and adverse drug reactions are the most important problems [2]. Some clinical and autopsy studies show significant reduction of β-cell function and mass in people with T2DM. Chronic hyperglycemia leads to an increased generation of reactive oxygen species (ROS), oxidative stress, and endoplasmic reticulum stress in a variety of cells. In comparison with many other cell types, the β-cells may be at exceptionally high risk of oxidative damage and an increased sensitivity for apoptosis [3, 4].

In recent years, studies on the benefits of natural products for human health have been increased. Honey bee products are also emphasized among natural products. These products are shaped according to the vegetation and floral diversity of the geography in which the honey bees are found. Honey bee products, including propolis, royal jelly, honey, bee venom, and bee pollen, or their bioactive chemical constituents like polyphenols, demonstrate interesting therapeutic potential in the regulation of inflammatory mediator production as the increase of TNF-α, IL-1β, IL-6, Il-2, and Il-7, and the decrease of ROS production. Additionally, improvement in the immune response via activation of B and T lymphocyte cells was reported both in vitro, in vivo and in clinical studies. Thus, the biological properties of bee products as anti-inflammatory, immune protective, antioxidant, anti-apoptotic, and antimicrobial activity have prompted further clinical investigation [5, 6]. The drugs are the powerfull agents for the treatment of the diseases. But, they all have side effects, clinically observed or not. Especially the side effects at the cellular level are frightening in terms of the cancer development, which is increasingly seen worldwide. Gliclazide is a second-generation sulphonylure commonly used for the treatment of T2DM. This drug act to reduce the blood glucose, by

stimulating the insulin release of the pancreatic β-cells. It is considered safe except that attention should be paid to its hypoglycemia effect. In practice, some very rare side effects with this drug are reported such as gastrointestinal disturbance, skin reactions, hematological disorders [7]. Cancer risk associated with sulfonylureas has not been extensively studied in comparison with other antidiabetic drugs; however, some studies indicate that there may be a higher incidence of cancer among those who receive oral antidiabetic drugs [8]. In this study, we aimed to evaluate potential harmful effects of gliclazide in human cell and to question if a natural product can improve this status. We used in this regard, the special products Anzer honey, pollen and propolis produced by bees in Anzer Plateau of Eastern Black Sea Region in Turkey. We evaluated the cytotoxic and genotoxic effect of gliclazide on Healthy Human Pancreatic Cell (hTERT-HPNE) and we investigated the results by adding Anzer honey, pollen and propolis in hTERT-HPNE containing gliclazide.

MATERIALS AND METHODS

Chemicals

Gliclazide was obtained from the local pharmacy in Ordu Turkey. Also 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from SERVA (Heidelberg, Germany), dimethyl sulfoxide (DMSO), Dulbecco's modified Eagle's medium (DMEM), ethanol, fetal bovine serum (FBS), penicillinstreptomycin, phosphate buffered saline (PBS), trypsin-EDTA, ultra salin were purchased from Thermo Fisher Scientific (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Annexin V-FITC/7-AAD Apoptosis Detection kit was purchased from Elabscience (USA).

Preparation of honey, pollen and propolis samples

The different quantities and types of Anzer honey, pollen and propolis samples were acquired from Anzer Plateau, Turkey in October 2021. Melissopalynological characterization was built using the uniformed technique improved by Louveaux et al. [9]. In this process, pollen was categorized with respect to percentages; preponderant, pollen effectuating 45% or more of the total pollen grains, secondary pollen (21–46%), significant minor pollen (5–17%), or minor pollen (less than 5%). Shortly, roundly 15 g of honey sample was unfreezed (75 mL) by the addition of 95% ethanol. The mixture was continually stirred with a shaker (Heidolph Promax 2020, Schwabach, Germany) at room temperature for 72 hours, and then sonicated for 4 hours with an ultrasonicator. The mixture passed through filter paper and concentrated in a rotary evaporator (IKA-Werke, Staufen, Germany) at 35°C. The residue was redissolved in ethanol and kept at 4°C until used for phenolic compound analysis.

Cell culture

The hTERT-HPNE cells were obtained from American Type Culture Collection (ATCC, Rockville, MD, USA). The hTERT-HPNE cells were cultured in 500 mL Dulbecco's modified Eagle's medium with 55 mL FBS (10%) and 0,1 mL penicillin/streptomycin (1%). The mediums were stored at +4°C and cells were removed by trypsinization. Cells were incubated in 5% CO_2 and 95% humidity at 37°C.

Cell viability and cytotoxicity

MTT test was performed to determine the viability of hTERT-HPNE. MTT test is a colorimetric assay by measuring colored formazan produce to assessing cell metabolic activity. Anzer honey, pollen and propolis were added to the hTERT-HPNE containing gliclazide at different doses depending on the cytotoxic effect. After determining the cytotoxic and non-cytotoxic doses of gliclazide, they were chosen for genotoxicity and apoptosis assessment in order of 1 mL gliclazide stock solution prepared newly in medium was used after filtered thanks to a 0,2 um millipor filter. Anzer honey, pollen, propolis stock solution were filtered and used in the similar method. The cultured cells were plated into 96-well plates with cells/well. After the incubation period of 24 hours, gliclazide was given to the cells at determined doses, and after one hour, Anzer honey, pollen and propolis were added at the determined doses. Gliclazide (24-0,187 mg/mL), Anzer honey, pollen, propolis (20-0,156 mg/mL) doses were given to the cells in appropriate volumes and incubated for 48 hours. Substance solutions were discarded at the end of the incubation period, 10 µL of 5 mg/mL MTT stock solution was additional to each well (final MTT concentration as 0.5 mg/mL) and were let, to incubate for 4 hours. To dissolve the formazan crystals formed in the wells, 100 µL of DMSO was added to each well. The absorbance values of the samples at 570 nm wavelength were measured in the spectrophotometer. Cytotoxicity was calculated by the percentage of the ratio between treated and untreated(control) cells(cell viability %). A blank and a sample/control were indicating the absorbance of blank and absorbances of samples or control separately. IC50 values of the compounds and the concentration decrease, the cell viability of treated cells by 50% with reference to the untreated cells were determined from the dose-response curves. Three independent assays were performed. The medium was used as negative control.

Percentage of cell viability (% cell viability) = (A samples–A blank) / (A control–A blank) x 100.

Apoptosis by flow cytometry

Cells were seeded in 25 cm^2 flasks containing $1x10^6$ cells each. Incubated for 24 hours at 37°C in 5% CO_2 to acclimate to the culture medium. As a result of the analysis made in the MTT test, when the various doses applied were compared, it was decided to use between the 3rd and 4th doses (Gliclazide 3 mg/mL) (Anzer honey, pollen, propolis 2.5 mg/mL). At the end of the incubation period, appropriate concentrations of gliclazide, Anzer honey, pollen, propolis were added to each well, and the cells were incubated for 48 hours. Then the cells were washed 2 times with 2 mL of cold PBS and 500 µL trypsin-EDTA solution was added to each well. Then, 50 µL Annexin V and 70 µL propidium iodide were added to hTERT-HPNE, then incubated for 15 min in the dark at room temperature. Stained hTERT-HPNE cells were analyzed by flow cytometry (BD FACSCalibur).

Gas chromatography/mass spectrometry analysis

Anzer honey, pollen and propolis components were determined with the aid of G/C-MS(G/C-MS-QP2010 Ultra Shimadzu brand) device. Restek- RTX-5MS column with thickness of 0.25 µm, diameter of 0.25 mm and length of 30 m was used for separation of target compounds. The temperature of column and injection port is 60 °C; 320 °C split injection was adopted. Samples were diluted 1/10 before being fed to the instrument. The evaluation of the samples was made qualitatively according to the % area distribution. Identification sample of peaks was used by W9N11 library.

Statistical analysis

Data show the mean of at least 3 independent experiments ± standard error mean (SE). GraphPad Prism 8 software (San Diego, CA, USA) software was used to perform the student's two-tailed t-test and for 2- way ANOVA analysis. P-values lower than 0.05 were considered statistically significant.

RESULTS

Cytotoxicity and cell viability

Gliclazide active ingredient (24-0.187 mg/mL) was diluted at the determined concentrations and exposed to the hTERT-HPNE for 48 hours. Decreases in cell viability were observed depending on the concentration during the exposure time. Cell viability decreased below 50% at concentrations of 3 mg/mL to 24 g/mL. The decrease in cell viability in 12 and 24 mg/mL were statistically significant when compared to the negative control ($p<0.05$). Gliclazide effect on cell viability of hTERT-HPNE was shown in figure 1. The IC50 value of hTERT-HPNE cells exposed to gliclazide for 48 hours was found to be 6 mg/mL. The gliclazide concentration was determined as 6 mg/mL to be used in other experiments.

Anzer honey, pollen and propolis were given separately to hTERT-HPNE cells by diluting them in certain volumes at determined concentrations (20-0.156 mg/mL) for 48 hours of exposure. It was observed that the cell viability decreased below 50% at a concentration of only 0.156 mg/mL in the pollen-treated cell. This decrease was significant when compared to the negative control ($p<0.05$). The IC50 value was found as 2.21 mg/mL in hTERT-HPNE cells exposed to pollen. It was observed that the cell viability decreased below 50% at concentrations of 0.312 mg/mL and 0.156 mg/mL in the propolis-treated cells. The two smallest concentrations of 0.156 mg/mL and 0.312 mg/mL were found to be significant when compared to the negative control ($p<0.05$). The IC50 value was found as 4 mg/mL in hTERT-HPNE cells exposed to propolis. It was observed that the cell viability decreased below 50% at the smallest three concentrations of Anzer honey-treated cells, and the three smallest concentrations of 0.156 , 0.312 and 0.625 mg/mL were found to be significant when compared to the negative control ($p<0.05$). IC50 value was found as 1.34 mg/mL in hTERT-HPNE cells exposed to Anzer honey. The effects of Anzer honey, pollen and propolis on hTERT-HPNE cell viability were shown in figure 2.

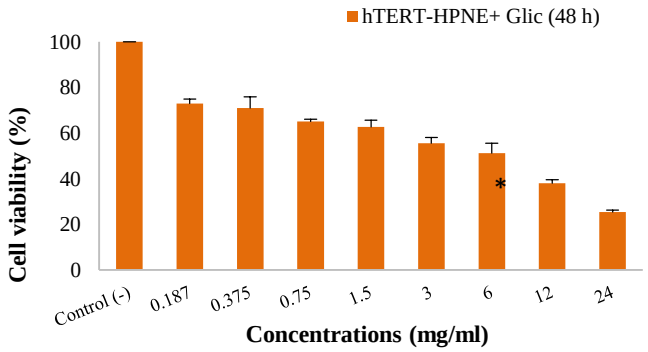

Figure 1. Gliclazide effect on cell viability of hTERT-HPNE.

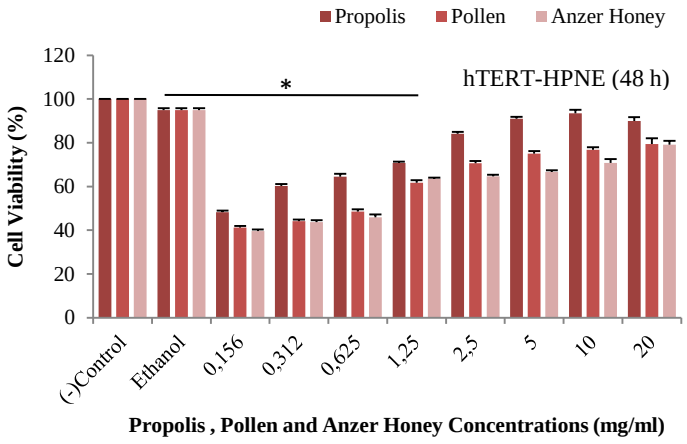

Figure 2. The Effect of Anzer honey, pollen, and propolis on hTERT-HPNE cell viability.

In order to improve the cytotoxic effect of gliclazide on hTERT-HPNE, determined concentrations (20-0.156 mg/mL) of Anzer honey, pollen, propoliswere given to the cell containing gliclazide active substance. After the 48 hours of exposures, it was observed that the cytotoxic effect of gliclazide was improved. When we applied propolis to the cell containing gliclazide active substance, a dose-dependent increase in cell viability was observed and no significant cytotoxic effect was observed. The concentrations with increased cell viability (12+10 mg/mL and 24+20 mg/mL) were found to be significant when compared to the negative control ($p<0.05$) The effect of propolis application on the cell viability of hTERT-HPNE containing gliclazide was shown in figure 3.

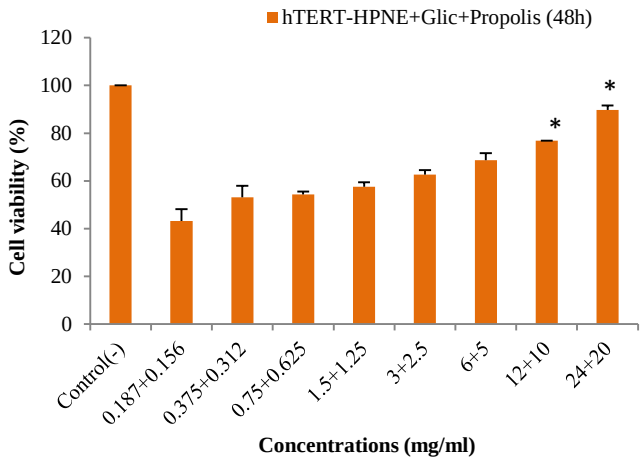

Figure 3. The effect of propolis application on the cell viability of hTERT-HPNE containing gliclazide.

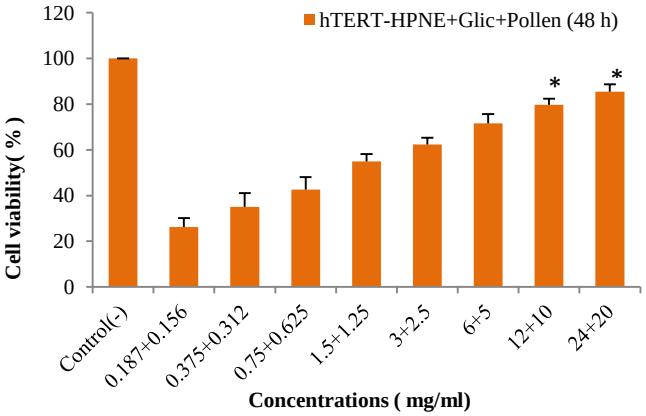

Figure 4. The effect of pollen application on the cell viability of hTERT-HPNE containing gliclazide.

When we applied pollen to the hTERT-HPNE containing gliclazide active substance, a dose-dependent increase in cell viability was observed and no significant cytotoxic effect was observed. The concentrations with increased cell viability (12+10 mg/mL and 24+20 mg/mL) were found to be significant when compared to the negative control ($p<0.05$) The effect of pollen application on the cell viability of hTERT-HPNE containing gliclazide was shown in figure 4. When we applied Anzer honey to the cell containing the gliclazide active substance, a dose-dependent increase in cell viability was observed and no significant cytotoxic effect was observed such as with pollen and propolis. The concentrations with increased cell viability 20+24 mg/mL) were found to be significant when compared with the negative control ($p<0.05$). The effect of Anzer honey application on the cell viability of hTERT-HPNE containing gliclazide was shown in figure 5.

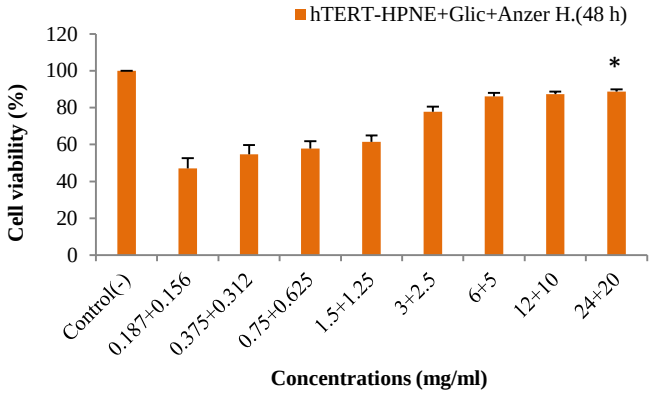

Figure 5. The effect of Anzer honey application on the cell viability of hTERT-HPNE containing gliclazide.

Apoptosis by flow cytometry

We performed apoptosis, necrosis and viability analysis by flow cytometry experiment on the groups that we treated with hTERT-HPNE containing gliclazide and Anzer honey, pollen, propolis for improvement. Images of this analysis were shown in figure 6. When we applied gliclazide at the concentration of 6 mg/mL, we determined in the MTT experiment, the rate of apoptosis in the hTERT-HPNE cell (40.66%) increased compared to the negative control (1.78 %). This rate was found to be statistically significant ($p <0.05$). Added pollen and propolis to the hTERT-HPNE cell caused a much less apoptosis increase compared to gliclazide own effect. The apoptosis rate was found to be 19.92% for pollen and 23.47% for propolis application and 30.75% for Anzer honey. These apoptosis rates were statistically significant ($p <0.05$) compared to gliclazide apoptosis rate on hTERT-HPNE. Anzer honey caused apoptosis in the hTERT-HPNE at a close rate of gliclazide. When Anzer honey, pollen and propolis were added to the hTERT-HPNE including gliclazide, it was determined that the apotosis created by gliclazide alone, decreased. The reductions in apoptosis rate were statistically significant for all the

treatment groups ($p < 0.05$) compared to gliclazide apoptosis rate on hTERT-HPNE The apoptosis rates of the treatment groups were shown in figure 6 and figure 7.

Chemical composition of Anzer honey, pollen and propolis

In this study, the main components (including fatty acids, unsaponifiables and volatile components) in Anzer honey, pollen and propolis extracted under optimal conditions were identified by G/C–MS. A total of 19 compounds were detected constituting 99.9% of the samples.

The main fatty acids detected were benzoic acid (11.06% in honey and 12.61% in pollen), n-hexadecanoic acid (14.21% in honey, 12.04% in pollen, 13.45% in propolis), octadecanoic acid (25.47% in honey, 23.06 in pollen, 30.89% in propolis) and pentadecanoic acid (9.94% in honey and 11.24% in pollen). Physicochemical properties of Anzer honey, pollen and propolis were analyzed according to Turkish national standards. Qualitative and quantitative analyzes of petroleum volatile profiles were listed in table 1 in order of elution.

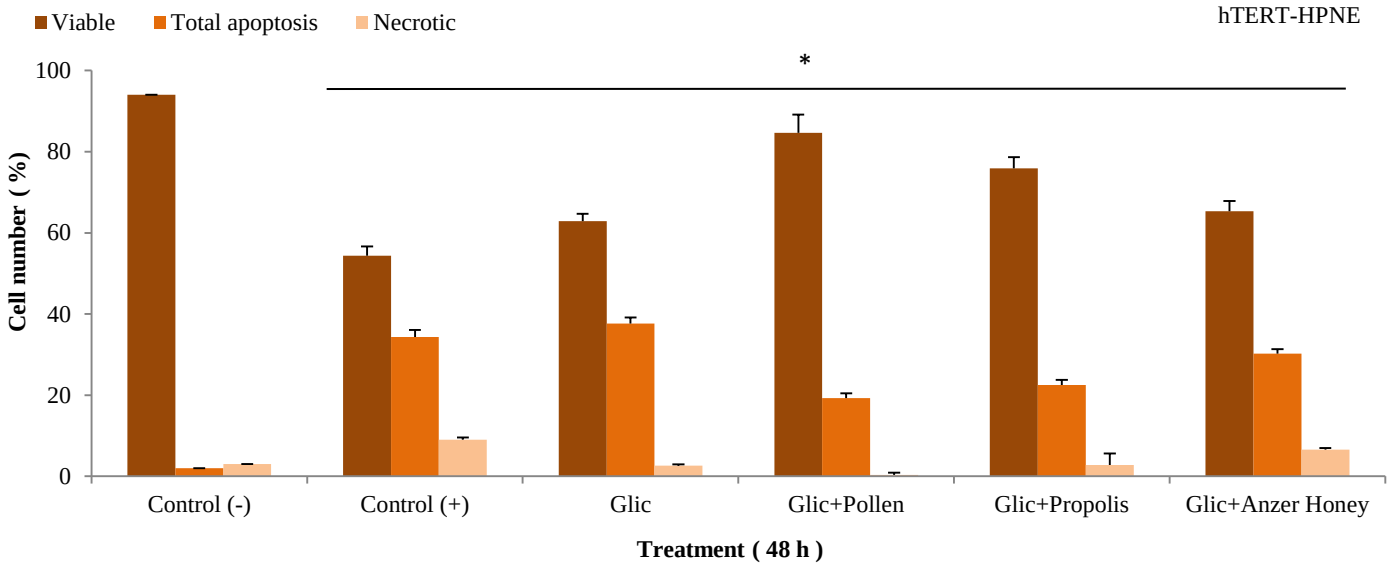

Figure 6. The apoptosis rates of the treatment groups.

Table 1 Analysis results of Anzer honey, pollen and propolis

HONEY				
R.T	**% area**	**Name**	**Cas no:**	**Sİ**
3.99	11.06	Benzoic Acid	65-85-0	98
10.874	14.21	N-Hexadecanoic Acid	57-10-3	95
12.889	25.47	Octadecanoic Acid	57-11-4	95
17.662	9.94	Pentadecanoic Acid, 2-Hydroxy-1-(Hydroxymethyl)Ethyl Ester	98863-1-5	85
POLLEN				
R.T	**% area**	**Name**	**Cas no:**	**Sİ**
3.989	12.61	Benzoic Acid	65-85-0	98
10.865	12.04	N-Hexadecanoic Acid	57-10-3	95
12.881	23.06	Octadecanoic Acid	57-11-4	95
17.658	11.24	Pentadecanoic Acid, 2-Hydroxy-1-(Hydroxymethyl)Ethyl Ester	98863-1-5	85
PROPOLIS				
R.T	**% area**	**Name**	**Cas no:**	**Sİ**
10.894	13.45	N-Hexadecanoic Acid	57-10-3	94
12.922	30.89	Octadecanoic Acid	57-11-4	92
16.03	8.45	4H-1-Benzopyran-4-One, 2,3-Dihydro-5,7-Dihydroxy-2-Phenyl-, (S)- (CAS)	480-39-7	76
25.047	14.49	Methyl Commate A	0-0-0	86

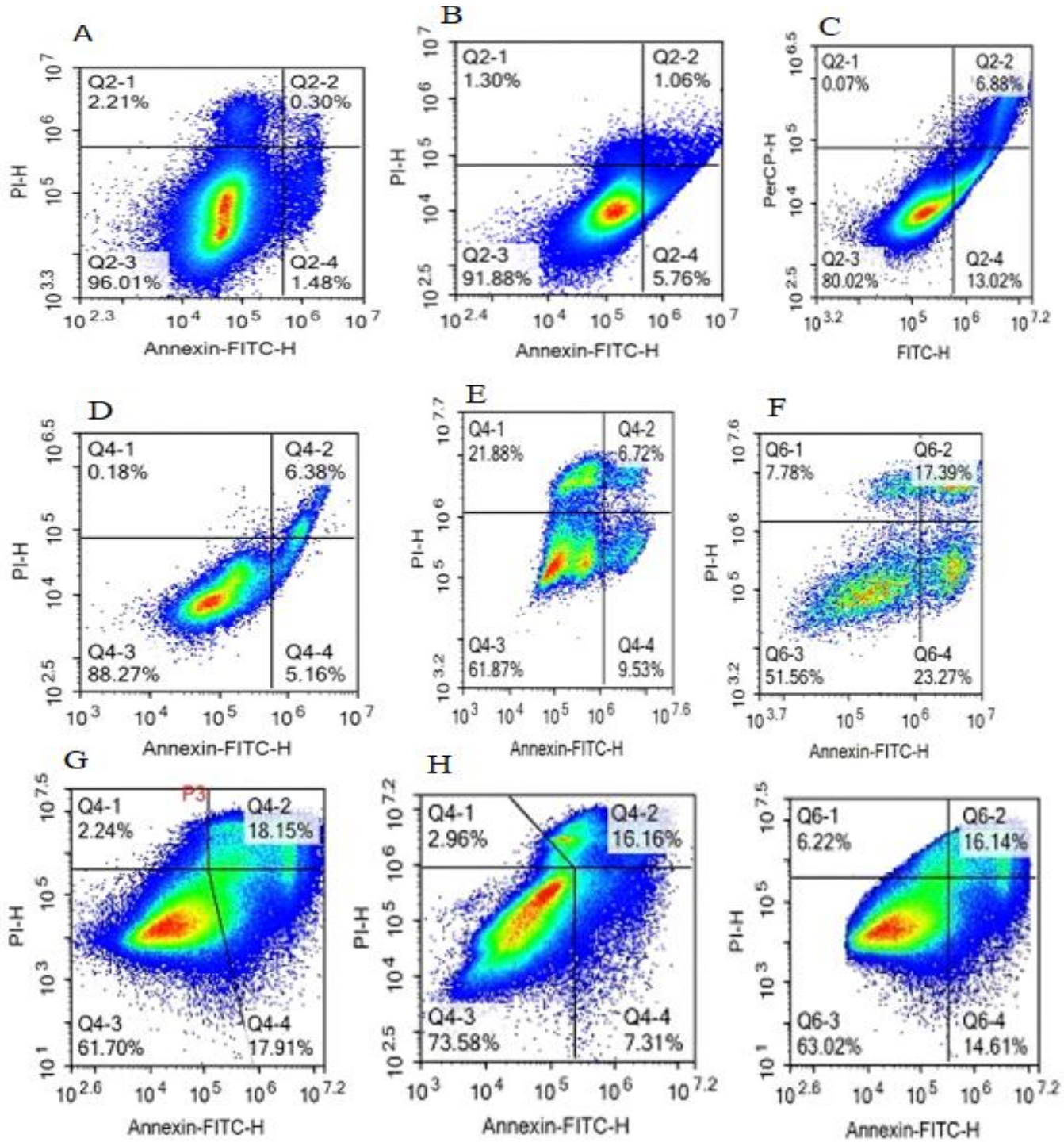

Figure 7. The apoptosis rates of the treatment groups.

DISCUSSION

The researches on the benefits of bee products continue to be up to date. Many studies observed some healing properties of bee products such as anti-inflammatory, antioxidant, anticancer, and immunomodulatory effects [10]. The drugs are the molecules with the similarities even more powerful effects, but they are not natural and have antigenic properties. Even though they have passed safety studies before the marketing, their long-term and regular use can lead to various

unpredictable side effects. The potential cancer development is one of the most life-threatening side effects. The incidence of cancer in diabetic patients is higher than that in the healthy population. Thus, the predisposing factors to the development of cancer in diabetes mellitus have been investigated [11]. Antidiabetic drugs have also been questioned in this regard and some studies mentioned that antidiabetic drugs can cause cancer [12].

The cytotoxicity and genotoxicity properties of the antidiabetic drugs have been investigated in some studies**.** In the study of Gul et al, sitagliptin (100mg/day), pioglitazone (30mg/day), rosiglitazone (4 mg/day) were evaluated. The genotoxicity was found higher in all the patients treated by these oral anti-diabetic agents than the diet-nutrition therapy (control) group. But, all of the three cytotoxicity endpoints were significantly lower in patients treated by these oral anti-diabetic agents compared with diet-nutrition therapy (control) group [13]. In the study of Kasurga et al, the peripheral lymphocytes were exposed to 125 µg/mL, 250 µg/mL and 500 µg/mL of vildagliptin and 250 µg/mL, 500 µg/mL and 1000 µg/mL of sitagliptin. No genotoxic effects were observed with these drugs and their metabolites, On the other hand, parallel to the increase in dose, vildagliptin showed weak cytotoxicity on the mitotic index, sitagliptin caused potential cytotoxicity and cytostatic effect on the mitotic index, nuclear division index and proliferation index [14]. In a study of Khan et al, the cell survival percentage (CSP) decreased upon treatment with sitagliptin (51% at 1000µg/mL), and produced damage to DNA with the threshold of above the 250µg/mL [15]. In the studies conducted on the relationship between sulfonylureas and cancer, some studies have indicated the increase of cancer risk with their use [16,17]. One study specifically mentioned the relationship of sulfonylureas with pancreatic cancer [18]. Another study mentioned the relationship of sulfonylureas with breast cancer [19]. However, in a review evaluating studies in recent years, it was stated that the use of sulfonylureas has no different cancer risk compared to the use of other oral antidiabetics [20]. There are many factors that affect the relationship between diabetes mellitus and cancer. The age, gender, familial cancer history, body weight, insulin resistance and other systemic diseases may be related to the cancer development [21]. However, the variety and difference effects of the drugs and the use of insulin were also questioned in this regard. A recent review notes that oral antidiabetics are weakly linked to cancer risk in most studies [22]. In the present study, the decreases in cell viability were observed depending to the concentrations of gliclazide. Anzer honey, pollen, and propolis had reducing effects on cytotoxicity, genotoxicity and apoptosis in the hTERT-HPNE cells. Also, these bee products increased cell viability and in addition, no cytotoxicity was observed. Furthermore, their curative effects were observed on the damage caused by gliclazide. The bee products are mentioned as rich in proteins, simple sugars, essential amino acids and omega fatty acids, which could explain their effectiveness in improving a health problem in human cells and tissues [23]. The bee products from different regions of the world may have different effects. In the study of Zullkiflee et al. some bee species found in Brunei were investigated and, it was observed that these bees products had antibacterial and antioxidant properties [24]. The natural products whose effects examined in this study are the products of bees found in the high altitude Plateau Anzer in Eastern Black Sea Region of Turkey**.** In the examination of the ingredients of these natural products with our previous research, we have detected many fatty acids (FAs) in their compositions [25]. We have found that some of the FAs in Anzer honey, pollen and propolis are common in all three natural products. FAs can modulate immune responses by acting directly on T cells and many of them are known to have antibacterial and antifungal properties [26]. Elevated levels of plasma FAs are important to contributor to insulin resistance, chronic inflammation, and other obesity-related disorders [27].

There are studies showing that the FAs have anticancer properties, and again the studies which mentioned the anticancer properties of bee products have indicated the FAs as responsible for this effect [28, 29]. Octadecanoic acid is one of the ingredients of bee products observed in this study. It is also known as stearic acid. Many in vitro and in vivo studies stated that stearic acid has some power especially in breast cancer to inhibit cancer cell proliferation, to induce apoptosis of tumor cells and even prevent cancer development [30]. The one of the FAs observed is n-hexadecanoic acid which is also known as palmitic acid. Many antitumoral effcts of palmitic acid were observed as apoptosis in tumor cells, inhibiting tumor cell proliferation, suppressing metastasis and invasion, enhancing sensitivity to chemotherapy, and improving immune function [31]. Benzoic acid also is a common FAs detected in bee products in this study. It is known to have some pharmacological properties. Benzoic acid and some of its derivatives have been found to have some effects as inhibiting tumor angiogenesis, inducing tumor cell apoptosis, and inhibiting cancer cell growth in some types of cancer [32]. This study has some limitations. It was conducted in vitro and the drug dosages were not used parallel to those used in clinical practice. In vivo and clinical studies may yield different results.

CONCLUSION

This study showed that Anzer bee products have cell-protective and vitality-enhancing properties. Our study is not against the use of the drugs, but the harmful effects of the drugs at the cellular level should not be ignored. These damages can cause new diseases over time. In this regard, further studies on the content and benefits of natural products in cell viability can give more definitive results and preliminary knowledge for future clinical trials.

DECLARATIONS

Author contributions

Conceptualization and writing: Ö.Ö., Ö.E. Methodology and analysis: Ö.E., Ç.Z. Investigation and editing: Ö.Ö., E.Ö.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Data availability statement

All data generated or analyzed during the study are included in this manuscript. Further inquiries can be directed to the corresponding author.

REFERENCES

[1] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, et al. (2019): Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9th edition. Diabetes Research and Clinical Practice, 157:107843 doi: 10.1016/j.diabres.2019.107843.

[2] Chaturvedi R, Desai C, Patel P, Shah A, Dikshit RK. (2018): An evaluation of the impact of antidiabetic medication on treatment satisfaction and quality of life in patients of diabetes mellitus.Perspectives in Clinical Research, 9: 15–22. doi: 10.4103/picr.PICR_140_16

[3] Evans JL, Goldfine ID, Maddux BA, Grodsky GM.(2002): Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocrine Reviews, 23: 599–622. doi: 10.1210/er.2001-0039.

[4] Rustenbeck I, Baltrusch S, Tiedge M.(2010): Do insulinotropic glucose–lewering drugs do more harm than good? The hypersecretion hypothesis revisited. Diabetologia, 53: 2105–2111. doi: 10.1007/s00125-010-1839-0.

[5] El-Seedi HR, Eid N, Abd El-Wahed AA, Rateb ME, Afifi HS, et al. (2022): Honey Bee Products: Preclinical and Clinical Studies of Their Anti-inflammatory and Immunomodulatory Properties. Frontiers in Nutrion,3:8:761267. doi: 10.3389/fnut.2021.761267.

[6] Giampieri F, Quiles JL, Cianciosi D, Forbes-Hernandez TY, Orantes-Bermejo J, et al. (2022): Bee Products: An Emblematic Example of Underutilized Sources of Bioactive Compounds. Journal of Agricultural and Food Chemistry, 70: 6833–6848. doi: 10.1021/acs.jafc.1c05822.

[7] Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, et al. (2004): GUIDE study: Double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. European Journal of Clinical Investigation, 34: 535–542. doi: 10.1111/j.1365-2362.2004.01381.x.

[8] Min Shin C, Kim N, Han K, Kim B, Jung JH et al. (2020); Anti-diabetic medications and the risk for colorectal cancer: A population-based nested case-control study. Cancer Epidemiology, 64(2) 101658 doi:10.1016/j.canep.2019.101658

[9] Louveaux J, Maurizio A, Vorwohl G. (2015): Methods of melissopalynology. Bee World, 59: 139-157. https://doi.org/10.1080/0005772X.1978.11097714

[10] Erdoğan Y, Dodoloğlu A. (2005): Importance of Pollen in Life of Honeybee (Apis meelifera L.) Colonies. Uludağ Bee Journal, 5: 79-84.

[11] Giovannucci E, Harlan DM, Archer MA, Bergenstal RM, Gapstur SM, et al. (2010): Diabetes and cancer: a consensus report. Diabetes Care, 33: 1674-1685. DOI: 10.2337/dc10-0666

[12] Wild SH. (2011): Diabetes, treatments for diabetes and their effect on cancer incidence and mortality: attempts to disentangle the web of associations. Diabetologia, 54: 1589-1592. DOI 10.1007/s00125-011-2169-6

[13] Gul OO, Cinkilic N, Gul CB, Cander S, Vatan Ö, et al. (2013): Comparative genotoxic and cytotoxic effects of the oral antidiabetic drugs sitagliptin, rosiglitazone, and pioglitazone in patients with type-2 diabetes: A cross-sectional, observational pilot study. Mutation Resarch,757: 31-35. DOI: 10.1016/j.mrgentox.2013.04.024

[14] Kasurka CB, Elbistan M, Atmaca A, Atlı Şekeroğlu Z. (2019): In vitro cytogenetic assessment and comparison of vildagliptin and sitagliptin. Cytotechnology, 71: 1063-1077. DOI: 10.1007/s10616-019-00345-y

[15] Khan HM, Nawaz H, Aerooj H, Sharif A. (2021): Genotoxic and cytotoxic assessment of sitagliptin and simvastatin alone and in combination. Pakistan Journal of Pharmaceutical Sciences, 34: 1939-1944. https://pubmed.ncbi.nlm.nih.gov/34836863/

[16] Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E. (2009): Sulphonylureas and Cancer: A Case-Control Study. Acta Diabetologica., 46: 279–284. DOI: 10.1007/s00592-008-0083-2

[17] Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin. (2006): Diabetes Care, 29: 254–258. DOI: 10.2337/diacare.29.02.06.dc05-1558

[18] Currie CJ, Poole CD, Gale EA. (2009): The Influence of Glucose-Lowering Therapies on Cancer Risk in Type 2

Diabetes. Diabetologia, 52: 1766–1777. DOI: 10.1007/s00125-009-1440-6

[19] Chen L, Chubak J, Boudreau DM, Barlow WE, Weiss NS, Li CI. (2017): Diabetes Treatments and Risks of Adverse Breast Cancer Outcomes Among Early-Stage Breast Cancer Patients: A SEER-Medicare Analysis. Cancer Research, 77: 6033–6041. DOI: 10.1158/0008-5472.CAN-17-0687

[20] Chen Y, Du L, Li L, Ma J, Geng X, et al. (2017): Cancer Risk of Sulfonylureas in Patients With Type 2 Diabetes Mellitus: A Systematic Review. Journal of Diabetes, 9: 482–494. 21. DOI: 10.1111/1753-0407.12435

[21] Zhu B, Qu S. (2022): The Relationship Between Diabetes Mellitus and Cancers and Its Underlying Mechanisms. Frontiers in Endocrinology, 11(13):800995 doi.org/10.3389/fendo.2022.800995

[22] Dankner R, Roth J. (2020): More recent, better designed studies have weakened links between antidiabetes medications and cancer risk. Diabetic Medicine, 37: 194-202. DOI: 10.1111/dme.14179

[23] Otreba M, Marek L, Stojko J, Rzepecka-Stojko A. (2026). Bee products as alternatives in the treatment of viral infections. Journal of the Science of Food and Agriculture, 1: 33-54. doi.org/10.1002/jsfa.70017..

[24] Zullkiflee N, Taha H, Abdullah NA, Hashim F, Usman A.(2022): Antibacterial and antioxidant activities of ethanolic and water extracts of stingless bees Tetrigona binghami, Heterotrigona itama, and Geniotrigona thoracica propolis found in Brunei. Philippine Journal of Science, 151: 1455–1462. Doi: 10.56899/151.04.13

[25] Özdemir Ö, Çöl Z, Ertürk Ö. (2023): Efficacy of Bee Products (Anzer Honey, Pollen and Propolis) in Detection and Healing of Damage Induced by Antidiabetic Drug Vildagliptin/Metformin Hydrochloride in Healthy Human Pancreatic Cells: Cytotoxic, Genotoxic and Biochemical Studies. Current Medical Science, 43: 1173-1182. doi: 10.1007/s11596-023-2812-8.

[26] Garcia C, Andersen CJ, Blesso CN. (2023): The Role of Lipids in the Regulation of Immune Responses. Nutrients,15(18): 3899. DOI: 10.3390/nu15183899

[27] Boden G. (2011): Obesity, insülin resistance and free fatty acids. Current Opinion in Endocrinology Diabetes and Obesity 18: 139–143. doi: 10.1097/MED.0b013e3283444b09.

[28] Biswas P, Datta C, Rathi P, Bhattacharjee A. (2022): Fatty acids and their lipid mediators in the induction of cellular apoptosis in cancer cells. Prostaglandins & Other Lipid Mediators,160:106637.doi:10.1016/j.prostaglandins.2022.106637.

[29] Sawicka D, Car H, Borawska MH, Nikliński J.(2012): The anticancer activity of propolis. Folıa Hıstochemıca et Cytobıologıca, 50: 25–37. doi: 10.2478/18693.

[30] Khan AA, Alanazı AM, Jabeen M, Chayhan A, Abdelhameed AS. (2013): Design, Synthesis and In Vitro Anticancer Evaluation of a Stearic Acid-based Ester Conjugate. Anticancer Research, 33 (6): 2517-2524. https://pubmed.ncbi.nlm.nih.gov/23749903/

[31] Wang X, Zhang C, Bao N. (2023): Molecular mechanism of palmitic acid and its derivatives in tumor progression. Frontiers in Oncology, 9,13:1224125. doi: 10.3389/fonc.2023.1224125.

[32] Anantharaju PG, Reddy BD, Padukudru MA, Chitturi MK, Vimalambike MG, Madhunapantula SV. (2017): Naturally occurring benzoic acid derivatives retard cancer cell growth by inhibiting histone deacetylases (HDAC). Cancer Biology &Therapy.,18(7):492–504.doi: 10.1080/15384047.2017.1324374.