Experimental Study / Deneysel Çalışma

Effect of royal jelly on serum trace elements in rats undergoing head and neck irradiation

Baş-boyun ışınlaması yapılan sıçanlarda serum eser elementleri üzerine arı sütünün etkisi

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Objectives: This study aims to investigate the effects of radiation on serum trace elements and the changes in these elements as induced by royal jelly in rats undergoing head and neck irradiation.

Materials and Methods: Thirty-two Sprague-Dawley male rats at the age of eight weeks with a mean weight of 275±35 g were included in the study. Subjects were divided into four groups with eight rats in each group: group 1: controls (C), group 2: radiation-only (RT), group 3: radiation plus royal jelly 50 mg/kg (RT+RJ50) and group 4: royal jelly 50 mg/kg-only (RJ50). Radiotherapy was applied to the head and neck area by single fraction at a dose of 22 Gy. The royal jelly was given once daily for seven days. The subjects were sacrificed on the seventh day of the study. Trace elements in blood samples were measured using ICP/MS method.

Results: When the trace element levels among the groups were compared using ANOVA test, a statistically significant difference was found in Al, As, Ca, Cd, Cr, K, Mg, Pb, Se, and Sn levels ($p<0.05$). No significant difference was found in the levels of Ag, Ba, Co, Cs, Cu, Fe, Ga, Hg, Mn, Na, Ni, Rb, Sr, Ti, U, V, and Zn ($p>0.05$). It was observed that oxidative stress was reduced in the radiation plus royal jelly group, compared to the radiation-only group.

Conclusion: Our study results suggest that head and neck irradiation increases oxidative stress, leading to some changes in the trace element levels, while royal jelly exhibits a protective effect against the oxidative stress induced by radiation.

Key Words: Head and neck tumor; radiotherapy; royal jelly; trace element.

Amaç: Bu çalışmada baş-boyun ışınlaması yapılan sıçanlarda radyasyonun serumda eser elementler üzerindeki etkisi ve bu elementlerdeki arı sütü ile ortaya çıkan değişiklikler incelendi.

Gereç ve Yöntemler: Çalışmaya 32 adet, sekiz haftalık ve ortalama 275±35 g ağırlığında Sprague-Dawley cinsi erkek sıçan alındı. Denekler her grupta sekizer adet olmak üzere, dört gruba ayrıldı: grup 1: kontrol grubu (K), grup 2: sadece radyasyon uygulanan (RT), grup 3: radyasyon ile birlikte 50 mg/kg arı sütü verilen (RT+AS50) ve grup 4: sadece 50 mg/kg arı sütü verilen (AS50) grup olarak belirlendi. Radyoterapi sıçanların baş-boyun bölgesine tek fraksiyonda 22 Gy doz olarak verildi. Arı sütü günde bir defa olmak üzere, yedi gün süreyle verildi. Çalışmanın yedinci gününde denekler sakrifiye edildi. Kan örneklerinde ICP/MS yöntemi ile eser element düzeyleri ölçüldü.

Bulgular: Gruplardaki eser element düzeyleri ANOVA testi ile karşılaştırıldığında Al, As, Ca, Cd, Cr, K, Mg, Pb, Se ve Sn düzeylerinde istatistiksel olarak anlamlı fark bulundu ($p<0.05$). Ag, Ba, Co, Cs, Cu, Fe, Ga, Hg, Mn, Na, Ni, Rb, Sr, Ti, U, V ve Zn düzeylerinde anlamlı farklılık bulunmadı ($p>0.05$). Radyasyon ile birlikte arı sütü verilen grupta, tek başına radyasyon uygulanan gruba kıyasla, oksidatif stresin azaldığı gözlendi.

Sonuç: Çalışma bulguları, baş-boyun ışınlamasının eser element düzeylerinde birtakım değişikliklere neden olup, oksidatif stresi artırdığını; arı sütünün ise, radyasyonun oluşturduğu oksidatif strese karşı koruyucu etkisinin olduğu göstermektedir.

Anahtar Sözcükler: Baş-boyun tümörü; radyoterapi; arı sütü; eser element.

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Radiotherapy is a commonly used treatment modality in head and neck tumors. Some side effects are observed in head and neck radiotherapy due to morphological, biochemical and metabolic changes that occur in healthy tissues. Frequently-seen acute side effects in patients undergoing head and neck irradiation include nausea, vomiting, weight loss, myelosuppression, mucositis, and malnutrition.[1-3]

The frequency and intensity of the side effects caused by radiotherapy may be associated with trace element amounts in the body. Trace elements play roles in many vital functions when they are in balance in the body. Examples for these include their function as antioxidants, as cofactors of several enzymes, their balancing function for membranes, assisting in functions of hormones, their protective role against minerals that are toxic to human health, assisting in the transport of several substances in the circulatory system, and repair and alleviation of wounds. Changes in trace element levels can decrease the effectiveness of antioxidant defense mechanism, leading to an increase in the negative effects of free oxygen radicals on cellular integrity. Consequently, it is thought that supplementing patients with diets containing necessary trace elements before, during and after treatment to minimize the side effects caused by radiotherapy may be highly beneficial as a supportive treatment and more and more studies are focusing on this subject.[4-10]

Royal jelly is a bee product secreted from the hypopharyngeal and mandibular glands of young worker bees to feed the young larvae and the mature queen bee. The composition of royal jelly may vary geographically and according to the climatic conditions and contains 60-70% water, 11-14% sugar, 4-5% lipid, 11-14% protein and 0.7-1.2% mineral and trace elements. It is rich in trace elements K, Ca, Fe, Na, Cu, Zn, and Mn. It is also rich in vitamins and contains niacin, thiamin, pantothenic acid, folic acid, inositol, biotin, pyridoxine and riboflavin. Many pharmacological activities of royal jelly were detected in experimental animals and clinical studies. Besides its anti-tumor, vasodilatative, hypotensive, anti-lipidemic, anti-thrombotic, immunomodulatory, anti-allergic, hypoglycemic, homeostatic and anti-oxidant effects, it has been demonstrated to prevent osteoporosis and augment wound healing and physical performance.[11-19] In addition to these, increasing proliferation and differentiation with a mitogenic effect on the cells, exhibiting a protective effect against the hematopoietic dysfunction caused by chemotherapy and radiotherapy and providing hemopoietic stem cell proliferation by granulocyte-macrophage colony stimulation and increasing collagen production in skin fibroblasts are the other effects of royal jelly demonstrated in studies.[20] In recent years several studies were published showing that royal jelly is effective in increasing the efficacy of radiation and chemotherapeutic agents commonly used in the treatment of cancer and in preventing normal tissue damage induced by treatment. Although there are studies on the effects of royal jelly on different organs and systems, very little information is available about its effect on trace elements.[13,15,19,21,22]

In this study, serum levels of the trace elements Al, Ag, As, Ba, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ga, Hg, K, Mg, Mn, Na, Ni, Pb, Rb, Se, Sn, Sr, Ti, U, V and Zn were investigated in order to show the effect of radiation on serum in rats undergoing head and neck irradiation, considering the available data.

MATERIALS AND METHODS

Approval for this study was granted by the Local Ethics Committee of Erciyes University School of Medicine for scientific research. Thirty-two healthy male Sprague-Dawley rats aged eight weeks and weighing 275±35 grams were used in the study. The rats were kept under standard laboratory conditions (12:12-hour light/dark cycle at 25±3 °C) and fed with commercial pelleted feed.

Experimental animals and study groups

The rats were divided into four groups with eight animals in each group. The groups were designed as follows:

Group 1: The control (C) group receiving no radiation or royal jelly,

Group 2: Radiation-only (RT) group,

Group 3: Radiation plus 50 mg/kg/day royal jelly (RT+RJ50) group,

Group 4: Royal jelly 50 mg/kg only (RJ50) group.

Radiotherapy administration

Radiotherapy was applied to the total cranium (to a 5x15 cm-area) using a Co-60 (Best Theratronics LTD., Ottawa, Ontario, Canada) device by single fraction at a dose of 22 Gy with rats in the prone position on a plexiglas table under ketamine anesthesia. Two rats were irradiated simultaneously. The radiotherapy scheme was based on the treatment used by Üçüncü et al.[22]

Royal jelly administration

Royal jelly used in the study was provided by Civan Beekeeping Limited Co. (Kayseri, Turkey). Immediately upon arrival, royal jelly was stored at -18 °C until being used in the study. When used in the study, royal jelly was dissolved in distilled water and orally administered to the rats at a dose of 50 mg/kg/day.

Blood samples and determination of trace element levels in serum

Intracardiac blood samples of 3-4 cc were taken on the seventh day of the study while the rats were under ketamine anesthesia. The collected blood samples were centrifuged at 3000 rpm for 10 minutes to separate the plasma. Blood samples of all groups were processed as described above and then stored at -20 °C until the analysis. The serum samples were thawed according to Berghof system before being read in inductively coupled plasma mass spectrometry (ICP-MS). For this purpose, 2 mL of serum sample was interacted with 5 mL HNO_3 and was thawed in a microwave oven under appropriate thawing conditions. Serum Al, Ag, As, Ba, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ga, Hg, K, Mg, Mn, Na, Ni, Pb, Rb, Se, Sn, Sr, Ti, U, V and Zn levels

Table 1. Trace element levels of the study groups

Trace elements	Control group	RT group	RT+RJ50	RJ50	*p*
Al	0.55±0.34^{2}	1.27±0.50^{1,4}	0.63±0.50	0.60±0.53^{2}	0.01
Ag	0.00±0.00	0.01±0.01	0.00±0.00	0.00±0.00	0.30
As	0.02±0.01^{2}	0.05±0.02^{1}	0.04±0.02	0.02±0.01	0.01
Ba	0.00±0.00	0.03±0.03	0.02±0.03	0.01±0.01	0.16
Ca	9.11±1.81^{2}	5.41±2.53^{1,4}	7.62±2.30	10.09±1.25^{2}	0.00
Cd	0.00±0.00^{2,3}	0.01±0.00^{1,4}	0.01±0.00^{1}	0.00±0.00^{2}	0.00
Co	0.02±0.06	0.18±0.49	0.00±0.00	0.00±0.00	0.42
Cr	0.09±0.04^{2,4}	0.04±0.02^{2}	0.07±0.03	0.04±0.01^{1}	0.02
Cs	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.60
Cu	0.66±0.22	0.43±0.09	0.88±0.55	0.68±0.54	0.20
Fe	1.97±0.84	2.68±1.20	1.56±1.16	2.01±2.07	0.47
Ga	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.37
Hg	0.00±0.00	0.00±0.01	0.00±0.00	0.00±0.00	0.12
K	38.31±13.62^{2}	62.37±10.37^{1,3}	35.69±11.05^{2}	47.56±13.07	0.01
Mg	6.98±1.43	4.98±1.45^{4}	5.56±1.91	7.49±2.12^{2}	0.02
Mn	0.04±0.08	0.02±0.03	0.02±0.02	0.06±0.07	0.51
Na	34.27±10.55	29.21±12.82	30.25±7.35	38.54±12.88	0.34
Ni	0.45±0.98	0.09±0.00	0.16±0.12	0.70±1.01	0.31
Pb	0.02±0.04	0.09±0.08^{3}	0.01±0.02^{2}	0.04±0.05	0.04
Rb	0.17±0.17	0.23±0.14	0.17±0.09	0.10±0.07	0.26
Se	0.24±0.09^{4}	0.19±0.03^{4}	0.24±0.13^{4}	0.39±0.06^{1,2,3}	0.00
Sn	4.10±1.96	6.60±2.51^{3,4}	2.34±1.27^{2}	2.54±1.59^{2}	0.00
Sr	0.28±0.21	0.26±0.16	0.19±0.11	0.17±0.08	0.42
Ti	18.19±3.55	27.32±19.97	27.69±15.38	25.38±15.43	0.55
U	0.01±0.00	0.01±0.00	0.01±0.00	0.00±0.00	0.27
V	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	1.00
Zn	0.42±0.08	0.34±0.07	0.34±0.04	0.46±0.32	0.40

C group: The control group receiving no radiation or royal jelly; RT group: Radiation-only group; RT+RJ50 group: Radiation plus 50 mg/kg/day royal jelly group; RJ50 group: Royal jelly 50 mg/kg only group; ^{1,2,3,4}: The differences between the groups having different figures at the same rows are significant ($p<0.05$).

were assessed with a ICP-MS device. The results were expressed in µg/dl.

Statistical analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) for Windows 15.0 statistical software was used for the analyses. One-way analysis of variance (One-way ANOVA) was used in the assessment the mean, standard deviation, highest and lowest values in the study groups and in the between-group comparisons; the groups showing differences were determined using Duncan's test. $P<0.05$ was accepted as statistically significant.

RESULTS

The mean (μg/dl) and standard deviation values for the trace elements measured in serum are presented in Table 1. Potassium, Na, Ti and Ca had the highest values in the C group and these values were 38, 34, 18 and 9 µg/dl, respectively. In the RT group K, Na, Ti and Sn had the highest values. These values were 62, 29, 27 and 9 μg/dl, respectively. In the RT+RJ50 group K, Na, Ti and Ca and in the RJ50 group K, Na, Ti and Ca elements had the highest values. These values were 35, 30, 27 and 6.6 µg/dl, respectively. In the RJ50 group these were 47, 38, 25 and 10 µg/dl, respectively.

In our study, Al, Ag, As, Ba, Cd, Co, Cu, Fe, Hg, K, Pb, Rb, Sn and Ti element levels in the RT group were higher when compared to the C group. The measured values for Ca, Cr, Mg, Mn, Na, Ni, Se, Sr and Zn were higher in the C group when compared to the RT group. Cr, Ga, U and V values were the same in both groups.

When the RT+RJ group was compared to the C group, the measured levels for Ca, Fe, Hg, K, Mg, Mn, Na, Ni, Pb, Se, Sn and Zn were higher in the C group, while Al, As, Ba, Cd, Cr, Cu, Rb, Sr, Ti and U levels were measured to be high in the RT+RJ50 group. The measured values of Ag, Co, Cs, Ga and V were the same in both groups.

When the RT+RJ50 group was compared to the C group, the measured levels of Ca, Fe, Hg, K, Mg, Mn, Na, Ni, Pb, Se, Sn and Zn were higher in the C group, while Al, As, Ba, Cd, Cr, Cu, Rb, Sr, Ti and U levels were measured to be higher in the RT+RJ50 group. The levels of Ag, As, Cd, Cs, Ga and V were found to be the same in both groups.

When the trace element levels were compared using ANOVA test, a statistically significant difference was found in the Al, As, Ca, Cd, Cr, K, Mg, Pb, Se and Sn levels ($p<0.05$). No significant difference was found in the levels of Ag, Ba, Co, Cs, Cu, Fe, Ga, Hg, Mn, Na, Ni, Rb, Sr, Ti, U, V and Zn ($p>0.05$).

In the study, it was seen that the serum Al, As, Cd and K levels for the RT group were significantly increased compared to the C group levels ($p<0.01$). The serum Al, As, Cd and K levels for the RT+RJ50 group were lower than those of the RT group. This difference was statistically significant in the C group. Moreover, there was a statistically significant difference in serum Al and Cd levels between the RJ50 group and the RT group. The serum Ca and Cr levels of the RT group were significantly lower when compared to the measured values of the groups receiving RJ50 ($p<0.001$). Moreover, the serum Ca level of the RJ50 group was higher than that of the C group. This difference was not statistically significant. The serum Mg level measured in the RT group was lower compared to the other groups. A statistically significant increase was observed in the serum Mg level in the RJ50 group compared to the RT group. Pb level measured in serum was increased in the group receiving radiation, while there was a significant decrease in the RT+RJ50 group. Selenium level was highest in the RJ50 group, while the group receiving RT had the lowest measured value. Moreover, a significant difference was found between the RT group and other groups in serum Se levels ($p<0.001$). It was observed that serum Sn level was increased in the group receiving radiation, while there was a decrease in the measured level in the group receiving RJ50 and RT+RJ50.

DISCUSSION

The use of chemicals for protection against the harmful effects of radiation began after World War II. Following the demonstration that normal tissue protection is as important as the destruction of cancer cells, studies focusing on protection research were conducted. For this purpose, many chemical compounds and their analogs were investigated for radioprotective effects. However, although patients tolerated natural nutritional agents better than other drugs, the nutritional agents used by humans have not received the attention that they deserve as potential radioprotectors.[2,3]

Almost all cancer patients develop malnutrition with time and require different forms of nutritional support. The effect of nutrition on survival and quality of life of cancer patients is important. Chemotherapy and radiotherapy as adjuncts to surgery lead to an increase in the existing malnutrition in cancer patients. Today, the nutritional therapies used to support cancer treatments are called "Nutritional Oncology Adjuvant Therapy." In this treatment program, the use of specific nutrients for different purposes such as support therapy, increasing tumor response and prevention of chemotherapy and radiotherapy complications draws attention. In addition, the anticarcinogenic properties of nutrients open new horizons in the administered treatments. In the light of all these data, the outlines of nutritional support protocols for use in cancer cases have become clear in the recent years. Above all, it was reported that nutritional support should complement the missing nutrients of the organism and provide benefit to the patient during radiotherapy and/or chemotherapy administration.[3,4,21,22]

Head and neck irradiation induces changes in the biochemical and physiological markers of the body. Ionizing radiation causes an increase in the production of reactive oxygen radicals (ROS) in tissues. These formed products increase lipid peroxidation and protein oxidation products by inducing the oxidation of macromolecules such as proteins, DNA and lipids. These resulting products mediate the destructive effect of ionizing radiation in biological systems. The toxicity induced by ROS may be eliminated by treatment with many exogenous and/or endogenous antioxidants in the body. It is known that trace elements play a role on ROS production and oxidant/antioxidant systems.[2-4] The changes in trace element levels are known to decrease the effectiveness of the antioxidant defense mechanism, leading to an increase in the negative effects of free oxygen radicals on cellular integrity. For example, the trace elements Cu, Fe, and Zn contribute to the detoxification of free radicals, while studies have demonstrated that Zn, Cu, and Mn have an important role in protection against cancer.[4,7,9,10]

The trace element amounts are closely related to several factors such as nutrition, age, disease and ecology. They are inorganic substances that contribute to catalytic, enzymatic and structural activities in many important events and they should be obtained exogenously from diet or water. Trace elements entering the body are distributed to all tissues by binding to several blood proteins. Up to 30 trace elements present in the body are known to play an important role in maintaining human health in a balanced way. It is possible to classify these elements, which play roles in biological functions in our body, into two subgroups, namely macro- and trace elements. If the amount required for the body is more than 100 mg/kg, these elements are called macroelement and this group includes elements such as Ca, Na, K, P, Mg, and Cl. If the amount required for the body is less than 100 mg/kg, these elements are called trace elements. These are elements like Mn, Se, Sn, Fe, Zn, Cu, I, Co, Al, As, Hg, Cd, Pb, and Ba.[6,9,10]

There are limited studies in the literature on the relationship between radiation and trace elements in serum in head and neck irradiation. In this study, the aim was to determine the serum trace element levels by ICP-MS method in order to show the changes in serum induced by radiation and to investigate the change induced by royal jelly in trace elements.

When the trace element levels in the groups were compared, a significant difference was found in Al, As, Ca, Cd, Cr, K, Mg, Pb, Se and Sn levels, while no significant difference was observed in Ag, Ba, Co, Cs, Cu, Fe, Ga, Hg, Mn, Na, Ni, Rb, Sr, Ti, U, V and Zn levels. The decrease in the amounts of basic elements Ca, Mg, Mn, Na, Se and Zn and the increase in the amount of trace elements toxic to human body, namely Ag, As, Cd, Co, Cu, Hg, Pb and Ti, suggested that these changes were associated with the change in the body induced by radiotherapy. Again, a significant difference was found in Ca, Cr, K, Mg, and Se levels in this group. The decrease in Na, Mg and Ca elements, which are macroelements of the body and play roles in many production functions in the body, was associated with the damage in cells induced by radiation and consequently to the utilization of these elements by cells to repair this damage. Another reason for the decrease in Na was considered to be the possible damage in Na-K pumps in the cell membrane. In the studies conducted, it was found that when there is impairment in this pump, a decrease occurs in cellular influx of sodium and cellular efflux of potassium, leading to a great amount of potassium accumulation within plasma.[23] Our results also showed that Na levels were decreased while K levels were increased in the radiotherapy group.

In our study, it was found that serum Fe levels increased whereas Ca levels decreased in the group receiving radiation when compared to the control group. In this study, copper level was observed to be higher in the group receiving radiation and royal jelly compared to the control group, whereas it was comparable between the group receiving royal jelly and the control group. In our study, the decrease in copper levels in rats exposed to radiation was associated with the negative change in serum trace element levels induced by radiation. The use of SOD enzyme, whose cofactor is Cu, for eliminating the negative effects of radiotherapy was thought to be the reason for this decrease. Different results were reported in several publications related to serum Fe and Cu levels. The increase in the amount of Fe was thought to be related to a damage in hemoglobin protein.[7,9] In the study of Silverman and Thompson[24] it was reported that there were no significant changes in serum Cu levels following radiotherapy in patients with oral or oropharyngeal cancer and in the healthy control group. In addition, although there are studies reporting an increase in Cu level following radiation administration, it is not clear whether this increase is a result or a cause and how it is increased.[10] Russanov et al.[25] reported that they observed an increase in the levels of SOD and CAT, for which Cu acts as a cofactor, as a result of radiation and this increase was caused by radiation and by the protective role of these enzymes against lipid peroxidation.

In this study, differences were found between the groups in Se levels. Se levels were found to be decreased in the group receiving radiation, whereas it significantly increased in the groups that received royal jelly. The reason for the decrease in selenium level was suggested to be its use for protecting the cell against free radical formation that occurs after radiotherapy. In some studies, serum selenium levels was reported to decrease following radiotherapy, while some other studies reported an increase.[8,10]

In this study it was observed that although Zn levels were different between the groups, they increased following royal jelly administration and the reverse was the case after exposure to radiation. Zinc plays an important role in cell membrane integrity, immune system function, cellular respiration, redox processes, protein synthesis and gene expressions of growth factors. It also breaks the free radical production chain by integrating into the structures of antioxidant enzymes and suppresses free radical formation by decreasing peroxidation rate. It was found to play an important role in the prevention of the side effects associated with radiotherapy.[4,7,24]

In this study, it was observed that royal jelly caused an increase in the levels of macroelements, which are required by the body, while decreasing the percentage in the body of the elements toxic to human body. According to this result, it was thought that several mechanisms were implicated in the radioprotective effect of royal jelly. Scavenging of radiation-mediated free radicals and the increase in cellular antioxidants induced by royal jelly are thought to be the main mechanisms responsible for this activity. Nagai et al.[16] found that the water and alkaline extracts of royal jelly possess antioxidant activity, protective activity against active oxygen species such as hydroxyl radicals and superoxide anion radicals and antioxidative activity. Jamnik et al.[26] reported that royal jelly increased mean survival and decreased oxidative damage in mice. Increase in the serum levels of Cu, Fe, and Zn, which are present in the structure of catalase, glutathione peroxidase and superoxide dismutase may be another mechanism involved in protection against radiation. Increasing this protective activity may also be effective in decreasing lipid peroxidation. In several studies, it was reported that royal jelly increased SOD, CAT, GSH-Px, and GSH groups and decreased lipid peroxidation. Furthermore, the protein fractions present in royal jelly were shown to possess high levels of antioxidant properties.[13,15,18,20]

In conclusion, it was seen that radiation caused a negative effect on trace element balance in addition to its structural and morphological damage to cells. Therefore, the addition of royal jelly as a food rich in trace elements both before and after treatment to minimize this effect of radiation during radiation treatment may be quite useful. As reported in many published studies investigating this topic, it was seen that royal jelly can be easily administered with diet, its use is safe and it is especially effective in preventing the side effects associated with radiotherapy. In the light of information gathered up to now, royal jelly could likely play an important role in the prevention and treatment of cancer.

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