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Effect of radiotherapy on erythrocyte catalase, and carbonic anhydrase activities, serum levels of some trace elements and heavy metals (Zn, Cu, Pb, Cd, Mn, Fe, Mg and Co) in cancer patients

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ABSTRACT

Background: We tried to reveal the relationship between the levels of some important minerals, rare elements and heavy metals by measuring serum cobalt (Co), lead (Pb), zinc (Zn), iron (Fe), copper (Cu), cadmium (Cd), magnesium (Mg), manganese (Mn), catalase (CAT) and carbonic anhydrase (CA) levels in head and neck, CNS, esophagus, stomach and breast cancers receiving radiotherapy. ***Materials and Methods***: Serum Cu, Fe, Pb, Zn, Co, Mg, Mn and Cd levels were measured using atomic absorption spectrophotometry. Carbonic anhydrase activity (CA), CO_2 hydration measurements were made using bromothymol blue method as indicator. ***Results***: Catalase activity, carbonic anhydrase activity and serum copper, lead, zinc, iron, cobalt, cadmium, manganese, magnesium measurements for baseline and post-radiotherapy values differ greatly in cancer patients compared to healthy subjects ($p<0.05$). ***Conclusion***: As a result, these findings have a significant impact on the pathophysiology of cancer. It can be argued that this paper shows a preliminary study for examining the effect of radiotherapy treatment on the activity of erythrocyte catalase, carbonic anhydrase and serum levels of cobalt, lead (Pb), zinc, iron, copper, cadmium, magnesium and manganese in the head and neck, CNS, stomach, esophagus and breast cancers receiving radiotherapy treatment.

INTRODUCTION

Oxidative stress can cause cancer formation. In such a situation, antioxidative activities are reduced [1, 2]. Catalase (CAT, H^2O^2: oxidoreductase, EC 1.1.11.1.6) is a metalloenzyme that decomposes hydrogen peroxide into molecular oxygen and water. CAT is a key enzyme effective in hydrogen peroxide metabolism [3]. CAT is one of the most common enzymes in plant, human and animal tissues. The most efficient enzymatic antioxidant processes involve catalase (CAT). It is a well-known plasma antioxidant and an effective scavenger of aqueous peroxide radicals [4,5]. Carbonic anhydrase (CA) (E.C. 4.2.1.1) is a member of metalloenzymes containing zinc in its active site [6,7,8]. A large number of CA isoenzymes and related proteins have been identified in humans and other animals. Nutritional status has a significant impact on the management of morbidity and entire prognosis in patients with head and neck cancer [9]. Radiation and chemotherapy are better tolerated by cancer patients. It has also been proven to be more effective in individuals with good nutrition [10,11]. Research has been conducted to obtain information about the levels of trace elements (such as Fe, Co, Zn, Mn, and Mg) in various body fluids in various diseases and the pathophysiology of diseases for the presence, management, and efficacy of diseases [12-16]. Carcinogenic elements are considered genotoxic or epigenetic carcinogens. Mechanical studies of metallic element carcinogenicity and biomonitoring of subjects acting on toxic metallic compounds are currently the main areas of research. Environmental pollution and cigarette smoke are risks for cancer [17].

Radiation therapy is applied on almost half of cancer patients. Radiation therapy can be used alone. It can also be used in conjunction with other cancer treatments such as surgery or chemotherapy. Although extensive research has been done on trace elements and heavy metals in normal cancer diseases, little research has been done on the concentration levels of these elements in pathological cancers such as head and neck, CNS, esophagus, stomach and breast cancers. This study aims to determine the importance of changes in serum trace element and heavy metal levels in head and neck, central nervous system, esophagus, stomach and breast cancers receiving radiotherapy compared to healthy controls.

MATERIAL AND METHODS

Biochemical analysis and radiotherapy application

Subjects were recruited from the outpatient clinics and inpatient ward of the Radiation Oncology Department of Yuzuncu Yil University Hospital. Simulation-purpose axial CT imaging were done on the Siemens Somatom Sensition4 model Computed Tomography (CT) then CT images were transferred to CMS XIO 4.34.02 treatment planning system via DICOM. All critical organs and target volumes contouring were drawn by a radiation oncologist. Treatment planning studies were controlled by a medical physicist and radiation oncologist. All patient groups were treated with a Cobalt-60 teletherapy (MDS Nordion) device adapted to a 3-dimensional (3D) conformal radiotherapy technique. The study included a total of 52 subjects, comprising of 37 cancer patients and 15 healthy individuals, with the characteristics shown in table 1. Blood samples were taken from patients and healthy individuals. Informed consent forms were obtained from patients and healthy individuals. The study was approved by the local ethics committee (registration number: 2009/16; date of registration: 06.05.2009).

The serum concentrations of Cu, Zn, Mg, Mn, Pb, Co, Cd, and Fe were determined by atomic absorption spectrophotometry (AAS) using a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK). CAT enzyme activity was measured according to the Aebi method [18] (Shimadzu UV-1201, Japan). CA enzyme activity was determined according to the Rickli and Wilbur-Anderson method [19].

Table 1. Cancer patients and healthy individuals' characteristics

Characteristics	Cancer Patients (n:37)	Healthy individuals (n:15)
Age, years		
Median	58	30
Range	19-78	20-41
Sex		
Male	18	13
Female	19	2
Primary sites of group		
Brain	5	
Head and Neck	9	
Breast	10	
Oesophagus	4	
Stomach	9	
Radiotherapy doses	45-70 Gy	
Median	50 Gy	
Radiotherapy duration	33-68 days	
Median	39 days	
Concomitant chemo radiotherapy	17	
Brain	1 (Temozolamide)	
Head and neck	2 (Cisplatin)	
Oesophagus	4 (5Fu+Cisplatin)	
Stomach	9 (5Fu+Leucoverin)	

Statistical analysis

In this study, one-way ANOVA was applied. In comparison, Student t-test was performed. Statistical significance was accepted as $P<0.05$. SPSS® statistical software package was used (SPSS for Windows version 13.0, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Serum Cu, Mg, Zn and Fe levels were lower in head-neck and CNS cancer patients before and after radiotherapy compared to healthy subjects ($P<0.05$). In patients with head and neck cancer, serum Cd, Pb and Co levels were higher before and after radiotherapy compared to the control group ($P<0.05$). Serum Mn level in patients with head and neck cancer was significantly lower than in healthy subjects before radiotherapy ($P<0.05$), however, it was higher in patients with cancer after radiotherapy than in the control group ($P<0.05$). The mean activities of CAT and CA were significantly lower in patients with head and neck and CNS cancer, both before and after radiotherapy, compared to the control group ($P<0.05$). Cu, Mg, Zn, and Fe serum levels and CAT and CAT activities were significantly lower in gastric cancer patients before and after radiotherapy than in healthy individuals ($P<0.05$). Serum Cd, Pb and Co levels in gastric cancer patients were higher both before and after radiotherapy compared to healthy individuals ($P<0.05$). Serum Mn level in gastric cancer patients was significantly lower before radiotherapy ($P<0.05$) and significantly higher after radiotherapy ($P<0.05$). Serum Mg, Zn, and Fe levels and CAT activity were lower in breast cancer patients before and after radiotherapy

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(P<0.05). Serum Mn and Pb levels in breast cancer patients were significantly lower before radiotherapy (P<0.05) and significantly higher after radiotherapy (P<0.05). Serum Co, Cd, and Pb levels in breast cancer patients were much higher both before and after radiotherapy compared to healthy individuals (P<0.05). CA activity in breast cancer patients before radiotherapy was significantly lower than in healthy individuals (P<0.05), but it was not significantly different in breast cancer patients after radiotherapy (p>0.05). Tables 2 and 3 show a summary of the results.

Table 2. Descriptive statistics and comparison results of healthy individuals between cancer patients before and after radiotherapy.

Parameters	Healthy individuals (control group, n:15)				Cancer Patients (initial values, n:37)				P*	Cancer Patients (after radiotherapy, n:37)				P*	P†
	Mean	SD	Maximum	Minimum	Mean	SD	Maximum	Minimum		Mean	SD	Maximum	Minimum		
Carbonic anhydrase (EU/gHg)$^{-1}$	2,0740	1,8070	5,1868	-4,5600	-0,6263	0,4609	1,3800	-0,8107	0,001	-0,7312	0,0380	-0,6551	-0,8003	0,005	0,140
Catalase (EU/gHg)$^{-1}$	44,0885	42,6955	183,5000	1,1470	0,8508	0,7850	3,4400	0,2300	0,001	2,1880	3,8920	14,9100	0,2300	0,001	0,186
Cd (µg/dl)	0,0037	0,0025	0,0080	0,0012	0,0189	0,0093	0,0460	0,0100	0,001	0,2161	0,1978	0,5000	0,0230	0,006	0,001
Pb (µg/dl)	0,0197	0,0264	0,0780	0,0010	0,1180	0,1448	0,7600	0,0050	0,005	0,2968	0,0597	0,3800	0,1700	0,001	0,001
Mg (µg/dl)	21,8287	0,6994	22,6400	20,5700	13,5950	5,6395	18,3600	1,8600	0,001	15,4600	3,2451	18,6100	8,1500	0,003	0,190
Cu (µg/dl)	1,2447	0,2709	1,6300	0,9200	0,6048	0,4200	1,4800	0,1420	0,003	0,9620	0,3938	1,8700	0,4700	0,004	0,021
Zn (µg/dl)	1,5313	0,1946	1,8900	1,2200	0,6623	0,1507	0,9500	0,3600	0,001	1,0680	0,2828	1,7300	0,5400	0,001	0,001
Fe (µg/dl)	2,3749	0,4807	3,0720	1,7600	0,9078	0,7489	2,7300	0,0700	0,001	2,4073	0,8588	4,3600	1,6100	0,001	0,001
Mn (µg/dl)	0,0270	0,0138	0,0490	0,0040	0,0042	0,0040	0,0160	0,0003	0,001	0,4996	0,2948	0,9500	0,1400	0,009	0,001
Co (µg/dl)	0,0005	0,0002	0,0009	0,0002	0,0341	0,0312	0,0940	0,0015	0,104	0,2952	0,3446	0,9700	0,0001	0,404	0,001

(*)Different from control group. (†) Different from initial values. SD: Standard deviation, Catalase (CAT), Carbonic anhydrase (CA), Copper (Cu), Lead (Pb), Zinc (Zn), Iron (Fe), Cobalt (Co), Cadmium (Cd), Manganese (Mn), Magnesium (Mg).

Table 3. Descriptive statistics and comparison results of healthy individuals between cancer patients groups before and after radiotherapy.

Parameters	Healthy individuals		Brain and Head and Neck cancer (n:14)				Breast cancer (n:10)				Oesophagus and Stomach cancer (n:13)			
	Control group(n:15)		Initially values		After Radiotherapy		Initially values		After Radiotherapy		Initially values		After Radiotherapy	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Carbonic anhydrase (EU/gHg)$^{-1}$	2,0740	1,8070	-0,740*	0,04	-0,740*	0,05	-0,740*	0,030	-0,740*	0,030	-0,530*	0,62	-0,720*	0,03
Catalase (EU/gHg)$^{-1}$	44,0885	42,6955	0,790*	0,91	2,070*	2,73	0,420*	0,310	4,760*	6,820	1,010*	0,79	0,580*†	0,35
Cd (µg/dl)	0,0037	0,0025	0,017*	0,0062	0,028†	0,0023	0,014*	0,0033	0,257*†	0,0427	0,0246*	0,012	0,3800*†	0,193
Pb (µg/dl)	0,0197	0,0264	0,090	0,0543	0,287†	0,0686	0,015	0,0102	0,345*†	0,0295	0,208*	0,196	0,278*	0,052
Mg (µg/dl)	21,8287	0,6994	8,193*	5,6629	16,472*†	1,9418	17,725*	0,6280	10,295*†	1,5757	16,519*	1,662	17,547*	0,583
Cu (µg/dl)	1,2447	0,2709	0,367*	0,3239	1,096*†	0,0506	0,395*	0,2977	1,437†	0,2501	0,9680	0,312	0,5433*†	0,169
Zn (µg/dl)	1,5313	0,1946	0,646*	0,1323	0,830*†	0,2372	0,583*	0,0778	1,279*†	0,3279	0,7270*	0,181	1,179*†	0,003
Fe (µg/dl)	2,3749	0,4807	0,592*	0,4922	1,903*†	0,8634	0,338*	0,1397	1,835*†	0,0809	1,566*	0,704	3,255*†	0,016
Mn (µg/dl)	0,0270	0,0138	0,001*	0,0011	0,523*†	0,2486	0,006*	0,0042	0,820†	0,3184	0,006*	0,004	0,284*†	0,051
Co (µg/dl)	0,0005	0,0002	0,023*	0,0307	0,116*†	0,0441	0,018	0,0134	0,907*†	0,0625	0,0551*	0,030	0,1080*†	0,041

(*)Significantly different from control group (p<0.05). (†) Significantly different from initially values (p<0.05). SD: Standard deviation, Catalase (CAT), Carbonic anhydrase (CA), Copper (Cu), Lead (Pb), Zinc (Zn), Iron (Fe), Cobalt (Co), Cadmium (Cd), Manganese (Mn), Magnesium (Mg).

DISCUSSION

Radiation therapy is applied to about half of cancer patients. Radiation therapy is used to treat cancers of the brain, larynx, breast, esophagus, stomach or other head and neck, and almost any type of solid tumor. Radiation therapy alone or in combination with other cancer treatments such as chemotherapy or surgery has been proven to be applicable. The goal of radiation therapy is to completely remove the entire tumor in cancer patients. For some cancer patients, the goal is to shrink one more tumor and reduce symptoms. The radiation dose used for a particular area depends on the type of cancer and various factors that may affect nearby tissues and organs that may be damaged by radiation.

In cancer cells, most therapeutic drugs act by causing increased levels of ROS production. As a result, it causes irreversible cell damage. Compromised antioxidant defense system causes further damage. ROS can occur at various stages of cellular metabolism. Cancer cells are metabolically active. It has been determined that the effect of oxidative stress in cancer cells is higher than in normal cells. Catalase reduces toxic hydrogen peroxide. Decreased CAT activity was demonstrated in some malignant tumor cells (25). We observed decreases in the activity of CAT in head and neck and breast cancer patients relative to control subjects both before and after radiotherapy (tables 2 and 3) (P<0.05). Previous research on CAT activity in gastric carcinoma has focused more on enzyme activity. Increased AOE activity has been detected in CAT in gastric cancers (26). However, patients with peptic ulcer and gastric cancer reported decreased serum CAT activity (27). We observed that serum CAT activity was significantly lower (P<0.05) in patients with gastric and breast cancer both before and after radiotherapy compared to healthy individuals. Therefore, CAT is a strong enzyme antioxidant. Carbonic anhydrase was shown to be effective in all cancers [6]. The authors observed that the activity of serum CA in head and neck cancer patients was lower than that of healthy subjects both before and after radiotherapy (tables 2 and 3) ($P<0.05$). The harmful effect of ionizing radiation has been demonstrated at in vivo studies that radiotherapy is effective in increasing reactive oxygen species in the organism. The authors observed that erythrocyte CA levels increased in gastric cancer patients both before and after radiotherapy compared to the control group ($P<0.05$). CA activity in breast cancer patients before radiotherapy was significantly lower when compared to healthy individuals. ($P<0.05$), but it was not statistically different after radiotherapy ($P<0.05$). CA in tumor cells is seen as a marker of acid -base balance in head and neck, stomach and breast cancers. Findings of this study prove this situation.

Zn fights against the harmful effects of free radicals. Zn deficiency may increase tumor proliferation. In one study, Zn levels decreased in breast cancer patients receiving radiotherapy [28]. In the literature, iron levels have decreased in patients with gastric cancer [29]. In another study in the literature, serum Zn levels in breast cancer patients were proven to be significantly lower than in control group [30]. In this study it was proven that serum Zn levels were significantly lower both before and after radiotherapy in general patients with head and neck cancer compared to healthy subjects (tables 2 and 3) ($P<0.05$). Serum Zn level in gastric and breast cancer patients was effectively lower than in healthy subjects both before and after radiotherapy ($P<0.05$). Depleted tissue-specific Zn absorption and gastrointestinal absorption can have significant effects and Zn is a very powerful antioxidant element. If zinc decreases, some cancers may develop in the body. Findings of this study confirm this situation [29].

Authors observed decreases in Fe levels before and after radiotherapy in patients treated for head and neck cancer compared to the control group (Tables 2 and 3) ($P<0.05$). We also found that serum levels of Fe decreased in stomach and breast cancer patients relative to control subjects both before and after the radiotherapy group ($P<0.05$). It has been claimed that low Fe levels can play an important role in the prevention of head and neck, stomach and breast cancers. Cu levels have been found to be elevated in patients with gastric cancer [29]. In breast cancer patients, serum Cu level before radiotherapy was effectively lower than in healthy subjects ($P<0.05$), but effectively higher after radiotherapy ($P<0.05$). Serum Cu determinations were important in assessing the clinical stage in head and neck, stomach and breast cancers. The serum level of Mg in breast cancer patients was lower than in healthy subjects both before and after radiotherapy (tables 2 and 3) ($P<0.05$). In a study conducted in the literature, it was proven that serum Cu levels in breast cancer patients are effectively higher than in control group [30]. High Zn and Cu homeostasis can be seen in head and neck cancer [31].

Mg consumption can be prophylactic against the onset of some cancers or neoplasms. In a study conducted in the literature, it was proven that serum Mg levels in breast cancer patients are effectively lower than in controls [32, 33]. Serum Mg levels in gastric cancer patients were extremely low both before and after radiotherapy compared to healthy individuals ($P<0.05$). In addition, serum Mg levels were significantly lower at patients with head and neck and CNS cancer before and after radiotherapy ($P<0.05$). Having a normal Mg level in the body can reduce the risk of developing cancer.

In one study, scalp Cd levels were decreased in gastric cancer [34]. Authors of this study proved that serum Cd levels in patients with head and neck, stomach and breast cancers were higher both before and after radiotherapy compared to healthy individuals (tables 2 and 3) ($P<0.05$). Further increase in serum Cd in cancer patients following radiotherapy may be due to Cd released from cells destroyed by the treatment. It has been proven in the literature that serum Co levels in breast cancer patients are effectively higher than in control group [32, 33]. Authors of this study observed that serum Co levels before and after radiotherapy were higher in patients with head-neck, stomach and breast cancers compared to the control group ($P<0.05$) (tables 2 and 3). Higher Co levels in head and neck, stomach and breast cancer patients can be a cause or the result of another unknown parameter.

In a study, the Mn level in the scalp decreased in stomach cancer [34]. Authors of this study observed that the serum level Mn was lower in head and neck, stomach, and breast cancer patients than in healthy individuals prior to radiotherapy, but was higher after radiotherapy (Table 2 and 3) ($P<0.05$). It has been proven in the literature that serum Mn levels in breast cancer patients are effectively higher than in control group [32, 33]. Also it was studied that the oxidative DNA damage (8-OHdG/106 dG rate) in the liver significantly increased with 5Gy radiation application in rats [35].

In a study, the Fe level in the scalp decreased in stomach cancer [34]. In another study, Fe levels were found to be high in gastric cancer [36]. This study proved that serum Fe levels before and after radiotherapy in patients with head-neck, stomach and breast cancers were lower than the control group ($P<0.05$) (tables 2 and 3).

In a study in the literature, Pb level was found to be high in gastric cancer, but not in statistically significant levels [36]. Authors of this study observed that serum Pb levels in patients with head and neck, stomach and breast cancers were higher both before and after radiotherapy than in healthy individuals

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(tables 2 and 3) (P<0.05). In addition, esophagus, head and neck, CNS, esophagus, stomach, breast cancers and stomach cancers are common worldwide [37]. Therefore, nutrition and diet play an important role in preventing cancer disease.

CONCLUSIONS

Zn may be protective against head and neck, CNS, esophagus, stomach and breast cancers. Authors propose that the changed heavy metal and trace element status of patients suffering from head and neck, CNS, esophagus, stomach and breast cancers may arise from increased requirements of cancerous serums for elements such as Cu, Mn, Pb, Cd, Fe, Zn, Co and Mg. Authors also suggest that carbonic anhydrase (CA) level in tumor cells can be a marker of acid-base balance in head and neck, stomach and breast cancers.

This study is the first to demonstrate the effect of radiotherapy in patients suffering from head and neck, CNS, esophagus, stomach and breast cancers.

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REFERENCES

1. Günes M, Eryilmaz R, Aslan R, Taken K, Demir H, Demir C (2021) Oxidant-antioxidant levels in patients with bladder tumours. *Aging Male, **5**: 1–6*.
2. Gündüz AM, Demir H, Toprak N, Akdeniz H, Demir C, Arslan A, Göya C (2021) The effect of computed tomography on oxidative stress level and some antioxidant parameters. *Acta Radiol, **62**: 260 -265*.
3. Glorieux C and Calderon PB (2017) Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new cancer treatment approach. *Biol Chem, **398**: 1095–1108*.
4. Harma M, Harma M, Erel O (2005) Measurement of the total antioxidant response in preeclampsia with a novel automated method. *Eur J Obstet Gynecol Reprod Biol, **118**: 47–51*.
5. Sayır F, Şehitoğulları A, Demir H, Aslan M, Çobanoğlu U, Bilgin C (2019) Serum prolidase activity, total oxidant/antioxidant, and nitric oxide levels in patients with esophageal squamous cell carcinoma. *Turk Gogus Kalp Damar Cerrahisi Derg, **27**: 206-211*.
6. Chu YH , Su CW, Hsieh YS, Chen PN, Lin CW, Yang SF (2020) Carbonic anhydrase III promotes cell migration and epithelial-mesenchymal Transition in oral squamous cell carcinoma. *Cells, **9**: 704*.
7. Demir H, Akkus ZA, Cebi A, Cakir T, Izmirli M (2010) Catalase, carbonic anhydrase and other biochemical parameters in esophageal cancers in Turkey. *Asian Pac J Cancer Prev, **11**: 1029-32*.
8. Tarun AS, Bryant B, Zhai W, Solomon C, Shusterman D (2003) Gene expression for carbonic anhydrase isoenzymes in human nasal mucosa. *Chem Senses, **28**: 621–629*.
9. Picker H and Bichler E (1985) Nutritional and immunological investigations in head and neck cancer patients before and after therapy. *Arch Otorhinolaryngol, **242**: 149–153*.
10. Hooley R, Levine H, Flores TC, Wheeler T, Steiger E (1983) Predicting post-operative head and neck complications using nutritional assessment: The prognostic nutritional index. *Arch Otolaryngol, **109**: 83–85*.
11. Doerr TD, Marks SC, Shamsa FH, Mathog RH, Prasad AS (1998) Zinc and nutritional status and clinical outcomes in head and neck cancer. *Nutrition, **14**: 489–495*.
12. Daila Bezerra LC, Mendes PMV, Melo SRS, Santos LR, Santos RO, Vieira SC, *et al.* (2021) Hypomagnesemia and its relationship with oxidative stress markers in women with breast cancer. *Biological Trace Element Research, **14**: 1-9*.
13. Fernandes G, Nair M, Onoe K, Tanaka T, Floyd R, Good RA (1979) Impairement of cell mediated immunity functions by diatery zinc deficiency in mice. USA; *Proc Natl Acad Sci, **76**: 457-461*.
14. Tessmer CF, Hrgovcic M, Thomas FB, Wilbur J, Mumford DM (1972) Longterm serum copper studies in acute leukemia in children. *Cancer, **30**: 358-365*.
15. Ilicin G (1971) Serum copper and magnesium levels in leukemia and malignant lymphoma. *Lancet, **2**: 1036-1037*.
16. Akkus I, Gürbilek M, Çalişkan Ü, Kaptanoğlu B, Üner A (1998) Blood and fingernail copper (Cu) and magnesium (Mg) Levels of children with acute lymphoblastic leukemia. *Tr J of Medical Sciences, **28**: 155-156*.
17. De Palma G, Goldoni M, Catalani S, Carbognani P, Poli D, Mozzoni P, *et al.* (2008) Metallic elements in pulmonary biopsies from lung cancer and control subjects. *Acta Bıomed, **79**(1): 43-51*.
18. Aebi H (1984) Catalase *in-vitro*. *Methods Enzymol, **105**: 121-126*.
19. Rickli EE, Ghazanfar SA, Gibbons BH, Edsall JT (1964) Carbonic anhydrase from human erytrocytes. Preparation and properties of two enzymes. *J Biol Chem, **239**: 1065-1078*.
20. Pelicano H, Carney D, Huang P (2004) ROS stress in cancer cells and therapeutic implications. *Drug Resis Upd, **7**: 97–110*.
21. Murata M, Suzuki T, Midorikawa K, Oikawa S, Kawanishi S (2004) Oxidative DNA damage is induced by a hydroperoxide derivative of cyclophosphamide. *Free Radic Biol Med, **37**: 793–802*.
22. Wagnerr T (1994) Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet, **26**: 439–456*.
23. Mazor D, Abucoider A, Meyerstein N, Kapelushnik J (2008) Antioxidant status in pediatric acute lymphocytic leukemia (ALL) and solid tumors: The impact of oxidative stress. *Pediatr Blood Cancer, **51**: 613–615*.
24. Sayır F, Şehitoğulları A, Demir H, Aslan M, Çobanoğlu U, Bilgin C (2010) Serum prolidase activity, total oxidant/antioxidant, and nitric oxide levels in patients with esophageal squamous cell carcinoma. *Turk Gogus Kalp Damar Cerrahisi Derg, **27**: 206-211*.
25. Demir H, Gürsoy T, Özkan H, Düzenli U, Sarıkaya E, Turan M, Kiroglu AF, Çankaya H (2018) Alterations in oxidative stress markers in laryngeal carcinoma patients. Bozan N. *J Chin Med Assoc, **81**: 811-815*.
26. Hwang TS, Choi HK and Han HS (2007) Differential expression of manganese superoxide dismutase, copper/zinc superoxide dismutase, and catalase in gastric adenocarcinoma and normal gastric mucosa. *Eur J Surg Oncol, **33**: 474-479*.
27. Tandon R, Khanna HD, Dorababu M, Goel RK (2004) Oxidative stress and antioxidants status in peptic ulcer and gastric carcinoma. *Indian J Physiol Pharmacol, **48**: 115–118*.
28. Mahmood Abdulrahman R, Abdullah Mohamad R, Abdulla Husam SK, *et al.* (2018) Estimation of Some Trace Elements and Antioxidant Status in Breast Cancer Patients Undergoing Radiotherapy. *Journal of Global Pharma Technology|, **10**: 213-217*.
29. Lin Y, Wu C, Yan W, Guo S, Liu B (2020) Five serum trace elements associated with risk of cardia and noncardia gastric cancer in a matched case–Control study. *Cancer Manag Res, **12**: 4441–445*1.
30. Choi R, Kim MJ, Sohn I, Kim S, Kim I, Ryu JM, *et al.* (2018) Serum trace elements and their associations with breast cancer subgroups in Korean breast cancer patients. *Nutrients, **11**: 37*.
31. Ressnerova A, Raudenska M, Holubova M, Svobodova M, Polanska H, Babula P, *et al.* (2016) Zinc and copper homeostasis in head and neck cancer: Review and meta-analysis. *Current Medicinal Chemistry, **23**: 13*.

[DOI: 10.52547/ijrr.20.1.15]

32. Abdelgawad IA, El-Mously RH, Saber MM, Mansour OA, Shouman SA (2015) Significance of serum levels of vitamin D and some related minerals in breast cancer patients. *Int J Clin Exp Pathol,* ***8****: 4074–4082*.
33. Mendes PMV, Bezerra DLC, Dos Santos LR, de Oliveira Santos R, de Sousa Melo SR, Morais JBS, *et al.* (2018) Magnesium in Breast Cancer: What ıs ıts ınfluence on the progression of this disease? *Biol Trace Elem Res,* ***184****: 334-339*.
34. Afzal A, Qayyum MA, Shah MH (2020) Study of trace metal imbalances in the scalp hair of stomach cancer patients with different types and stages. *Biol Trace Elem Res,* ***196****: 365-374*.
35. Cakir T, Yildizhan K, Huyut Z, Uyar A, Arihan O (2020) Radioprotective profile of Urtica dioica L. seed extract on oxidative DNA-damage in liver tissue and whole blood of radiation-administered rats. *Braz J Pharm Sci,* ***56****: e18382*.
36. Feng L Du J, Yao C, Jiang Z, Li T, Zhang Q, *et al.* (2020) Ribosomal DNA copy number is associated with P53 status and levels ofheavy metals in gastrectomy specimens from gastric cancer patients. *Invoroment Interantional,* ***138****: 1-11*.
37. Taya SW, Lia JW, and Fock KM (2021) Diet and cancer of the esophagus and stomach. *Current Opinion Gastroenterology,* ***37****: 158-163*.

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