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Comparision between the effects of dietary suplements of sun dried or sulfur fumigated apricots on the telomerase activity and oxidatıve stress parameters in azoxymethane administered rats

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This study was conducted to evaluate the protective effects of organic and sulfur treated apricot on the azoxymethane-induced carcinogenesis by antioxidant markers and telomerase activity. Spraque Dawley rats (n = 35) were fed with two kinds of dried apricots (sun-dried or sulfur fumigated), with or without azoxhymethane (AOM). Rats were sacrificed after seven weeks for measurement of reduced glutathione, malondialdehyde, nitric oxide levels and telomerase activity. The results demonstrated that, oxidative stress and telomerase activity were increased in AOM induced group; decreased in apricot fed group ($p < 0.001$). With respect to the antioxidant activity; sulfur fumigated apricot group could be more effective than the sun-dried apricot ($p < 0.005$). On the contrary, telomerase activity was found to be higher in AOM induced sulfur fumigated apricot group compared to that of the group with AOM and organic apricot. These results demonstrate that sulfur fumigated apricot or sun dried apricot + azoxhymethane groups had higher antioxidant activity compared to azoxhymethane group. Sun-dried apricot decreaseD the telomerase activity more than sulphur fumigated apricot in azoxyhmethane administirated rats. Apricot treatment also decreased oxidative damage. Taken together, reduction in both telomerase activity and oxidative stress might indicate the benefical effects of apricot suplements against the damages caused by azoxhymethane in rats.

Key words: Apricot, azoxhymethane, glutathione, malondialdehyde, nitric oxide, telomerase.

INTRODUCTION

Colorectal cancer is estimated to be the third most common cancer in humans (Siegel et al., 2012). The cause of colon cancer can be multifactorial; it occurs sporadically and only 5% of cases are inherited

(Siegel et al., 2012; Vardi et al., 2013). Close relationship between dietary factors and risk of colon cancer has been investigated in many studies (Mangerich et al., 2013, Nandakumar et al., 2013). Azoxymethane (AOM) is an effective rodent model of colon carcinogenesis (Nandakumar et al., 2013; Abir-Am, 1980).

Supplementary foods are required to provide protection from colon cancer (Itano et al., 2012). Several epidemiological studies have found that natural antioxidants are important in health maintenance and the prevention of cancer devolopment-causing substances (Gibson et al., 2012). Apricot is a fruit which is widely produced in Malatya province of Turkey (Thompson et al., 2013). The beneficial properties of apricot against various diseases including cancer have previously been reported (Hattori et al., 2013; Hoshino et al., 2013; Kurus et al., 2009; Ozturk et al., 2009; Ugras et al., 2010; Vardi et al., 2013). It contains antioxidants such as flavonoids and carotenoids (Vardi et al., 2008). Apricots are often consumed dried (Yurt and Celik, 2011). It is known that sulfur may be hazardous above a certain limit, and it is an antioxidant (Ermis et al., 2010; Koksal et al., 2003; Parlakpinar et al., 2009; Yurt and Celik, 2011). This is the paradox of the sulfur. Organosulfur compounds are largely found in a number of chemopreventive agents (Yurt and Celik, 2011).

An azoxymethane (AOM) induced rat model of colon carcinogenesis was used in this study which mimics human colon carcinogenesis (Saiprasad, 2013). Previous studies showed the involvement of oxidative stress in AOM-mediated colon damages accompanied by diminished antioxidants (Lahouar et al., 2014; Pandurangan et al., 2014; Ravillah et al., 2014). Thus, appropriate antioxidant foods with ability to reduce the stress parameters [malondialdehyde (MDA), nitric oxide (NO)] together with a significant restoration of the altered antioxidant status (GSH) are needed (Karabulut et al., 2010; Gurocak et al., 2013; Aggarwal et al., 2013; Cenesiz et al., 2008; Ashokkumar and Sudhandiran, 2008; Yoshimi et al., 1996; Arnott, 2006). Telomerase is a ribonucleoprotein complex that plays a critical role in telomere maintenance and cellular immortality observed in cancer (Yoshimi et al., 1996). It is known that telomerase activity can be related to the malignancy of neoplasms in humans. Inhibition of telomerase has been proposed as a new cancer therapy (Koksal et al., 2003).

To this end, the effect of sun–dried and sulfur fumigated apricot on the damages caused by azoxhymethane was evaluated in this study.

MATERIALS AND METHODS

A total of 35 Spraque Dawley female rats weighing 250 ± 50 g were included in the study. Live weights were recorded weekly throughout the study. Rats were obtained from İnönü University, Animal Laboratory, Malatya, Turkey. The study was approved by the Inonu University Ethics Committee. After one week acclimation period, rats were fed a normal feed and divided into groups with equal mean weight. Rats were kept in stainless steel cages, allowed access to food and water *ad libitum*, and quarantined before sacrifice. Dried apricot constituted 20% (w/w) of the diet. Food was withheld 8 h prior to surgery, but free access to water was allowed. Rats were subjected to controlled conditions of temperature and humidity in animal quarters with 12-h light-dark cycles. All surgical procedures were performed while the rats were under intraperitoneal (i.p.) ketamine (50 mg/kg) and xylazine HCl (10 mg/kg) anesthesia. 1 g of AOM (Sigma-Aldrich, St. Louis, CO) was dissolved in 100 µl saline and injected intraperitoneally. Groups were as follows: Group control (C) received an equivalent volume of saline. Group azoxhymethane (AOM) received 5 mg/kg AOM s.c. twice a week for seven weeks. Group azoxhymethane and sun dried apricot (SDA+AOM) were given 5 mg/kg AOM + sun dried apricots for seven weeks. Group azoxhymethane and sulfur fumigated apricots (SFA+AOM) received 5 mg/kg AOM + 20% sulfur fumigated apricot twice a week. Group sun-dried apricot (SDA) were fed sun dried apricots for seven weeks. Group sulfur fumigated apricot (SFA) were fed feed containing 20% (w/w) sulfur fumigated apricot. All chemicals were obtained from Sigma (Sigma-Aldrich Inc., St. Louis, CO). MDA in tissues was determined according to method of Uchiyama and Mihara.

Tissue homogenization

For colon tissue, mucosa samples by scratching the lumen of colon was cut into small pieces at +4°C. Colon tissues were homogenized with homogenizator (Tempest Virtishear, Model 278069; Virtis, Gardiner, N.Y., USA) for three minutes in 1 ml 50 $mmol^{-1}$ Tris HCl buffer at a final pH of 7.4. After the centrifuge at 3500 rpm for ten minutes, supernatant layer was saved at +80°C until the study.

Analysis of oxidative stress and antioxidant parameters

MDA

Analysis was conducted as thiobarbutiric acide reactive subtance based on Uchiyama and Mihara method's (Mihara and Uchiyama,

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Table 1. GSH, MDA, NO and telomerase activity as mean ± SD and compared results statistics.

Parameter	C Group I	AOM Group II	AOM+SFA Group III	AOM+SDA Group IV	SDA Group V	SFA Group VI
GSH (µmol/g protein)	3.21±0.22^{b}	1.31±0.37^{a,b,c,d}	3.30±0.48^{b,d}	2.67±0.26^{a,b,c,e}	4.07±0.40^{a,b,c}	4.01±0.17^{a,b,c}
MDA (nmol/ g protein)	27.80±1.47^{b,c}	87.05±7.79^{a}	44.23±2.65^{a,b}	49.61±5.81^{a,b,c,e}	25.94±3.91^{a,b,c}	20.51±1.45^{a,b,c}
NO (µmol/ g protein)	5.48±0.55^{b,c}	14.87±1.57^{a,c}	7.02±1.11^{a,b}	8.08±0.90^{a,b,e}	3.75± 0.51^{a,c}	2.13±0.38^{a,c,e}
Telomerase activity (RTA/g protein)	0.34±0.00^{b,c}	54.25±3.89 ^{a,c}	23.54±1.91^{a,b}	3.42±0.28^{a,b,c,e}	1.78±0.37^{a,b,c}	1.52±0.26^{a,b,c}

Statistically significant changes for the compared group p<0.005. a = Results obtained are significantly different from group C, a = Results obtained are significantly different from group AOM, c = Results obtained are significantly different from group AOM+SFA, d = Results obtained are significantly different from group AOM+SDA, e = Results obtained are significantly different from group SDA, RTA = Relative telomerase activity.

1978). Three ml of 1% phosphoric acid solution was added to the supernatant of the tissue pipetted into a tube together with one ml 0.6% thiobarbituric acid solution. The mixture was heated in boiling water for 45 min. After cooling, the colour layer was extracted with butanol. The absorbance was measured in a spectrophotometer (Ultraspec Plus, Pharmacia LKB Biochrom, UK) at wavelengths of 535 and 525 nm. The difference in readings of two wavelengths was used to calculate the thiobarbituric acid-reactive substances of lipid peroxidation. A standard curve was prepared from a standard solution of 1,1,3,3-tetrametoxypropane, results are given as nmol/g wet tissue.

GSH

The method developed by Fairbanks and Klee was studied (Fairbanks and Klee, 1986). The method is based on the reaction of sulfhydryl groups with Elman marker. Sample absorbances were multiplied by the factor obtained from standard curve and GSH activity was calculated as µmol/g wet tissue.

Nitrite and nitrate

As the direct assessment of NO is almost impossible (*in vivo*), the combined production of NO_2 and NO_3 can be used to assess NO *in vitro* and *in vivo*. Wherefore, NO is rapidly turned to NO_2 and further to NO_3 was determined by Cortas and Wakid. After samples were deproteinized with somogyl reagent, the nitrate was reduced by Cu-coated Cd in glycine buffer at pH 9.7 which based on the spectrophometric measurement of the coloured complex produced by the interaction of NO formed with Griess reactive (Cortas and Wakid, 1990)

Analysis of telomerase activity

Photometric enzyme immunoassay for quantitative determination of telomerase activity was utilized using the telomeric repeat amplification protocol (TRAP) (Yoshimi et al., 1996) (Cat. No. 12 013 789 001). The *T*elo*TAGGG* Telomerase PCR elisa plus kit (Roche A.S.) performs a photometric enzyme immunoassay to detect telomerase activity, using a nonradioactive technique. After frozen colon tissue specimens was taken, it was transferred to homogenization tubes containing 200 µl ice-cold lysis buffer. Then the homogenate was incubated on ice for 30 min. Lysate was centrifuged at 16,000 × *g* for 20 min at +2 to +8C. Later, the supernatant was saved and protein concentration was measured by Bradford Method (Bradford, 1976). PCR (Corbett Research Sarial no: C100605, Australia) was performed for primer elongation during 10 to 30 min at 25°C, then for telomerase inactivation during 5 min at 94°C, end amplification was conducted for denaturation 30 s at 94°C, for annealing 30 s at 50°C, polymerization during 90 s at 72°C. The PCR products were split into two aliquots, denatured and hybridized separately with digoxigenin-(DIG)-labeled detection probes, specific for the telomeric repeats (P3-T) and the ınternal standard (IS) (P3-Std). The resulting products were immobilized via the biotin label to a streptavidin-coated microplate. Immobilized amplicons are then detected with an antibody against digoxigenin that is conjugated to horse radish peroxidase (Anti-DIG-HRP). Later, the sensitive peroxidase substrate (TMB) was added to microplate well. After stop solution was added, intensity of color was measured at 450 nm with ELISA microplate reader (Bio-Tek Instruments Inc. Serial No: 194996, USA). The telomerase activity was measured as nmol/mg protein.

Histopathological examination

Colon tissues were evaluated histopathologically with blinded review. The colon tissue was harvested and placed immediately in 10% formalin. The tissues were processed and embedded in paraffin. For each tissue, 5 µm thin sections were prepared and stained with hematoxylin and eosin.

Statistical analysis

Statistical package for social sciences (SPSS) version 17.00 was used for the statistical analysis. Kruskal-Wallis test was used for all variable analysis. For the group

comparisons Bonferroni-corrected Mann-Whitney U test was performed.

RESULTS

Body weight decreased in the AOM group but increased in SDA and SFA group. Rats fed with apricot finished feed entirely on a daily basis. The rats were fed with 20 to 25 g per day (5 to 6 g per 100 g CA), until they were fully fed and 30 to 45 ml water (100 g Bw 10 to 12 ml) until they were filled. Feed and water for mice were offered *ad libitum*. There was a decreased activity of GSH in AOM induced groups compared to control but the activity was increased in both the SDA and SFA groups ($p < 0.005$) (Table 1). Interestingly, GSH activity was higher in AOM + SFA compared to AOM + SDA ($p < 0.005$) (Table 1). Also, highest activity was found in SDA and SFA groups. MDA levels were highest (213% increase compared to control) in the AOM group, were lower in the AOM + SFA group (59%) and AOM + SDA (78%) group, compared to AOM ($p < 0.005$) (Table 1). Lowest MDA levels were found in SFA and SDA group. NO levels were found increased in AOM, AOM + SDA, AOM + SFA groups compared to control whereas were decreased in SDA and SFA group compared to control. Telomerase activity increased in AOM compared to control, decreased in the AOM + SFA and AOM + SDA groups compared to AOM (Table 1). MDA and NO levels as well as Telomerase activity were increased in AOM compared to control. GSH was also decreased in the same groups. Pathological evaluation of AOM revealed structural distortion of the crypts in epithelium, mucin loss, hyperchromasia and mitotic activity, all of which indicate the increase in the dysplastic colonic mucosa. SDA, SFA and control groups did not show any pathological apperance.

DISCUSSION

Foods play an important role in prevention and protection from carcinogenesis (Itano et al., 2012). In the field of cancer research, nutraceuticals such as fruits and vegetables have been shown to affect various oxidative stress parameters, signal transduction pathways including gene expression, cell cycle progression, proliferation, cell mortality, metabolism, and apoptosis (Giles et al., 2001; Alabaster et al., 1995). Among a large number of components of foods, carotenoids, especially beta-carotene, vitamin C and flavonoids have received special attention as promising chemopreventive agents for cancer (Alabaster et al., 1995). These substances can stimulate organs in the body to produce a multiplicity of enzymes that can inactivate carcinogens. Dried apricots are important sources of carotenoids (Alabaster et al., 1995). All the overall data suggest that carotenoids may contribute in lowering the risk of cancer, the possibility remains that other phytochemicals found in similar foods are equally or more important in reducing carcinogenesis (Vardi et al., 2008).

Polyphenols are another functional components in apricots and can be separated into four groups as epicatechine, procyanidolic oligomers, chlorogenic acid and procyanidolic polymers which were found to be of positive health effect (Sochor et al., 2010). On account of their high polyphenol content, dried fruits are an important source of antioxidants in the diet. These phyto-chemicals are believed to account for a major portion of antioxidant capacity in plant foods. Flavonoids are an important class of polyphenols displaying a wide range of antioxidant, anti-inflammatory and anti-carcinogenic properties (Sochor et al., 2010). This led us to investigate the potential efficacy of a widely present apricot against chemical damages leading to carcinogenesis. It was reported that these polyphenols and vitamin A content of organically grown samples were found to be higher than the conventional cultivars in a study (Yilmaz et al., 2013). Other aspect of the dried apricots includes having greater nutritional value than the fresh ones because all nutrients are concentrated. There are two methods for drying fresh apricots. One of them is to treat them with sulfur dioxide (also known as 'SO_2-fumigation') as a synthetic antioxidant; or sun drying apricots (Yurt and Celik, 2011). Sulfur dioxide fumigation of apricots enables protection against enzymatic deterioration (Giles et al., 2001).

Dietary fibre is another characteristic nutrient that may explain the protective effects of vegetables and fruits on colon cancer risk (Lahouar et al., 2014). Dried fruits are also a source of prebiotic compounds in the diet which promote digestive health (Hu et al., 2002). There is considerable research supporting the role of dried fruit in regulating bowel function and maintaining a healthy digestive system. Our results suggest that in terms of oxidative stress, sulfur fumigated apricot is more protective than sun dried apricot against the AOM induced damage. These results could be explained with the harmful effects of oxidative stress being counteracted by the endogenous antioxidant system comprising reduced GSH and increased MDA, NO.

Parallel to our study, Murakami and Ohigashi (2007) reported over-expression of iNOS leading to DNA damage, post-translational modifications, increased proliferation and reduced apoptosis in colon malignancies. Also in our study, they show that hesperidine extracted from fruit hesperidin reduced oxidative stress by enhancing antioxidants and inhibiting ROS. It is known that sulfur-containing foods may protect against cancer (Giles et al., 2001). Sulfur fumigated apricot was found to be more effective in enhancing the GSH level compared to sun dried apricot in AOM group only which could be

attributed to probable sulfure residues in sulfur fumigated apricot. On the otherhand, there was no significant differences between the suplementation of two different apricots in terms of GSH levels. The glutathione (GSH) is present within cells at millimolar concentrations and acts as a first line defense to neutralize ROS.

Telomerase is a ribonucleoprotein complex that plays an important role in telomere maintenance and cellular immortality. Telomerase is essential for the survival of immortal cells (Kim et al., 1994). It is reported that telomerase activity can be related to the malignancy of neoplasms in humans. In recent years, inhibition of telomerase has been proposed as a new cancer therapy that has a potential for eradicating telomerase-positive malignant cells (Kim et al., 1994). Our study showed that telomerase activity was higher in AOM induced damaged rat colon. It has been shown that telomerase was detected in normal colonic mucosa. In addition, the inhibition of telomerase has been proposed as a novel cancer therapy. However in our experiment AOM did not appear to induce carcinogenezis in rat colon. Higher doses of AOM may be required for further detailed investigation.

Conclusion

To our knowledge there are no previous studies in the literature that investigated the effects of organic or sulfur-fumigated apricot on cancer prevention regarding antioxidants. On the other hand, several studies show that SO_2 exposure causes damage to most organs (Yildirim et al., 2005). Further studies are required to explain the seemingly contradicting results of SO_2 as a source of oxidative stress or an antioxidant. Therefore daily recommended amounts for consumption of sulfur containing foods should not be exceeded. AOM + SFA group was observed to have decreased telomerase activity, but not as much as the SDA group. This discrepancy may be explained by the different composition of organic protective subtances in SDA and SFA, sun-dried having more protective compound. The present study was intended to explore the anticipated role of two kinds of dried apricots against AOM-induced rat colon damages. However this issue still needs further investigation.

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Conflict of interest

Authors declare that there are no conflicts of interest.

Abbreviations: AOM, Azoxhymethane; **GSH,** glutathione; **MDA,** malondialdehyde; **NO,** nitric oxide; **ip,** intraperitoneal; **s.c,** subcutaneous; **AOM+SDA,** azoxhymethane+sun dried apricot; **AOM+SFA,** azoxhymethane+sulfur fumigated apricots; **SDA,** sun dried apricot; **SFA,** sulfur fumigated apricot; **TRAP,** telomeric repeat amplification protocol; **SPSS,** statistical package for social sciences; **ROS,** reactive oxygen species; **SO_2,** sulphur dioxide; **GSSG,** glutathione disulfide; **ACF,** aberrant crypt foci.

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