RESEARCH COMMUNICATION

Plantago major Protective Effects on Antioxidant Status after Administration of 7,12-Dimethylbenz(a)anthracene in Rats

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Abstract

Aim: The present study was designed to evaluate effects of *Plantago major* extract on oxidative status in Wistar albino rats administrated 7,12-dimethylbenz(a)anthracene (DMBA). **Methods**: Rats were divided into three equal groups of 6 animals each: Group 1 controls, group 2 treated with DMBA (100 mg/kg, single dose) and group 3 receiving the DMBA and the aqueous extract at 100 mg/kg/d for 60 days. **Results**: Significant decrease in catalase ($P<0.05$), carbonic anhydrase ($p \leq 0.01$), reduced glutathione (GSH) ($P<0.01$) and total protein ($P<0.01$) values was observed in the DMBA group compared with the healthy controls and DMBA + *Plantago major* groups. **Conclusion**: The results suggest preventive effects of Plantago major on DMBA induced oxidative damage in Wistar albino rats that might be due to decreased free radical generation.

Keywords: Antioxidant - DMBA - lipid peroxidation - *plantago major* - rat

Introduction

Polycyclic aromatic hydrocarbons (PAH) are organic pollutants that are released into the environment in large quantities, mainly due to human activities (Neef, 1985). 7,12- Dimethylbenz(a)anthracene (DMBA) is one of polycyclic aromatic hydrocarbons chemical group. DMBA is known as carcinogenic (Hsue et al., 2008), mutagenic (Donovan et al., 2004), cytotoxic (Burchiel et al., 1992) and immunosuppressive (Lichius and Muth, 1997) agent. Although the risk for cancer is multifactorial, a substantial portion of cancer incidence rates is related to environmental factors, including diet and exposure to certain chemicals (Singletary et al., 1997).

In the organism are produced free radicals during several intracellular pathways and are increased during infection, inflammation and exposure to pollutants, ionizing radiation and sunlight. Oxidative stress generated from free radicals in turn oxidizes and damages several proteins and DNA, leading to genomic instability and cancer (Laviano et al., 2007; Ozben, 2007). DMBA have been shown to form free radicals and these compounds play a critical role in carcinogenesis (Cavalieri et al., 1978). This role is accompanied by the generation of reactive oxygen species, such as peroxides, hydroxyl and superoxide anion radicals, which induce cellular oxidative damage through DNA strand breaks and lipid peroxidation (Nagata et al., 1985; Kodama et al., 1989; Batcioğlu

et al., 2002). Furthermore, there are some antioxidant defense systems responsible for detoxifying free radicals whose concentration increases depending on various reasons. Those systems are composed of enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and nonenzymatic compounds such as glutathione (GSH) and albumin. If the sensitive balance between the levels of free radicals and the members of the antioxidant defense system is disturbed, this may cause for many pathological changes leading to the cell and tissue damage (Burton et al., 1985).

There is great clinical interest in oxidative stress and lipid peroxidation, due to the suggestion that many significant disease states are associated with oxidative injury. MDA is commonly used as a marker for the lipid peroxidation process (Claeson et al., 2000).

Carbonic anhydrase (CA) catalyzes the reversible hydration of carbon dioxide (CO_2) to bicarbonate (HCO_3^-) (Khalifah, 2003). CA is found in several tissues such as lung, liver, kidney and brain. This enzyme not only regulates the pH of several media in organisms, it also indirectly involves in the antioxidant enzyme system (Denicola et al., 1996). It is reported that CA functions as an oxyradical scavenger and thus protects cells from oxidative damage and CA over expressing cells exhibit lower free radical levels (Raisanen et al., 1999).

Epidemiological data indicate that frequent consumption of certain vegetables, fruits, spices, teas,

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herbs and medicinal plants suppress carcinogenesis in various organs (Dekker and Verkerk, 2003; Sengupta et al., 2004). *Plantago major* is a perennial plant that belongs to the Plantaginaceae family (Samuelsen, 2000). It is renowned as a traditional herbal medicine throughout the world. P. major, a popular traditional cure that has been used for many diseases (Mc Cutcheon et al., 1995). *Plantago major* has shown to contain five classes of biologically active compounds, namely flavonoids (baicalein, baicalin, luteolin), phenolic compounds (caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid), benzoic compound (vanillic acid), iridoid glycoside (aucubin) and triterpenes (oleanolic acid, ursolic acid) (Samuelsen., 2000). P. major has been used in ulcers treatments (Yesilada et al., 1993), against skin problems and gastrointestinal disorders (Samuelsen., 2000), diuretic agent (Caceres et al., 1987). Furthermore, it has been indicated that P. Major's herbal tea can show free radical scavenger effect (Campos and Lissi., 1995). Experimental studies have proven that this plant has antitumoral (Yaremenko., 1990; Lithander., 1992), analgesic and antiinflammatory (Nunez et al., 1997), antibacterial (Moskalenko., 1986), antifungal (McCutcheon et al., 1994) and antigiardiasic (Macotela., 1994) properties.

The aim of the present study was to investigate the chemopreventive effect of *Plantago major leaf extract* on levels some biochemical parameters with MDA, GSH, carbonic anhydrase and catalase in Wistar albino rats subjected to DMBA.

Materials and Methods

Plant materials

Plantago major samples were collected from Van, Turkey and authenticated in Department of Biology in Faculty of Science, Yuzuncu Yil University, Van. Plant material dried at room temperature. Dried material (300 mg) was infused in 30 mL of boiled distilled water for 30 min. After decantation and filtration, the filtrate was again dried in an incubator at a temperature of 50°C. The aqueous extract was then prepared in isotonic physiological solution (Bnouham et al., 2003).

Experimental protocol

All procedures described were studied and approved by the Local Institutional Committee for the Ethical Use of Animals. Wistar albino rats were maintained in a room with a constant temperature of 22 ± 1°C, a relative humidity of 55 ± 10%, and a 12-h light/dark cycle. They were maintained with free access to water and a standard laboratory diet. This study was performed on 18 Wistar albino rats. Rats were divided into three equal groups. Group 1 was control group (n=6), given orally olive oil (intragastrically). Group 2 (n=6), rats treated with a single dose of DMBA (100 mg kg-1) in olive oil given orally (intragastrically). Group 3 (n=6) was treated with a single dose of DMBA (100 mg kg-1) in olive oil followed by aqueous extract of *Plantago major* 100 mg kg-1 per day given orally (intragastrically) for 60 days. Blood samples (serum/plasma) were collected for biochemical studies.

Biochemical estimations

The levels of MDA formed in whole blood were assessed by measuring the concentration of thiobarbituric acid reactive substances (Sushil et al., 1989). Levels of GSH was measured in whole blood by the method of Beutler et al., (1963). Biochemical analysis of CAT activity in erythrocytes was performed with a method described by Aebi (1984). CA activity was assayed by hydration of CO_2. The hydration of CO_2 was measured by the method of Rickli and Wilbur-Anderson with bromothymol blue as indicator (Rickli et al., 1964). The levels of total protein, albumin, glucose and creatinin in serum were measured in autoanalyser equipment by using commercial Kit (Abaxis Diagnostics Ltd India).

Statistical analysis

Data were analyzed in Statistical Analysis System (SAS, 2010). To compare of group means was used one-way analysis of variance and duncan multiple comparisons test by Sas Proc Glm procedure. For descriptive statistics was used Proc Means in SAS.

Results

No death was observed in any of the experimental groups. Changes in MDA, GSH, Total protein, albumin, glucose and creatinin levels with CAT and CA activity of the control, DMBA-treated and aqueous extract of Plantago major treated groups are presented in Table 1 ($\overline{X}$ ±SEM) and Figure 1-5.
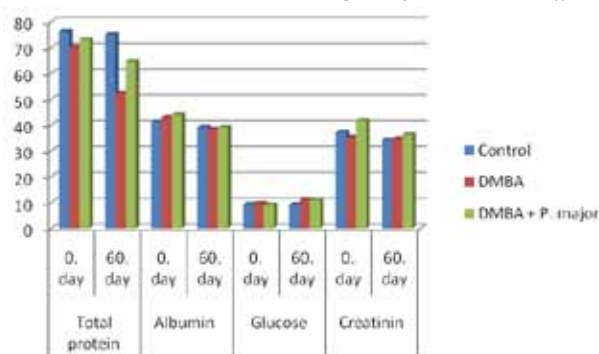
Levels of total protein, albumin, glucose and creatinin

O. Day data analyses showed that between the levels of parameters were not found statistically significant. After 60 days data analyses indicated a significant decrease

Table 1. The Average Levels of Total Protein, Albumin, Glucose, Creatinin, MDA and GSH with Activities CA and CAT of Control, DMBA and DMBA + *P. major* groups

| Groups	0. Day ($\overline{X}$ ± SEM)			60. Day ($\overline{X}$ ± SEM)		
	Control	DMBA	DMBA + PM	Control	DMBA	DMBA + PM
Total Protein (g/L)	76.3 ± 3.14	70.2 ± 2.83	73.2 ± 3.09	75.0 ± 2.25[b]	52.3 ± 2.92[b,b1]	64.5 ± 4.85[b1]
Albumin (g/L)	41.2 ± 2.27	43.0 ± 0.45	44.0 ± 2.11	39.2 ± 1.97	38.3 ± 1.98	39.0 ± 2.34
Glucose (mmol/L)	9.40 ± 0.46	9.72 ± 0.67	9.08 ± 0.34	9.27 ± 0.45	11.2 ± 0.99	11.0 ± 0.68
Creatinin (mmol/L)	37.3 ± 5.28	35.3 ± 4.72	41.7 ± 2.62	34.3 ± 1.87	34.8 ± 1.30	36.3 ± 2.23
MDA (nmol/ml)	1.05 ± 0.18	1.02 ± 0.12	1.41 ± 0.19	0.91 ± 0.09[a]	4.16 ± 0.50[a,a1]	1.02 ± 0.08[a1]
GSH (mg/dl)	0.04 ± 0.004	0.04 ± 0.005	0.04 ± 0.003	0.04 ± 0.001[b]	0.03±0.002[b,b1]	0.04 ± 0.003[b1]
CA EU/(gHb)$^{-1}$	0.33 ± 0.009[c]	0.34±0.01[c,c1]	0.26 ± 0.03[c1]	0.34 ± 0.008[b]	0.28 ± 0.02[b,b1]	0.35 ± 0.01[b1]
CAT EU/(gHb)$^{-1}$	69.0 ± 8.24	39.4 ± 2.58	55.7 ± 15.5	71.6 ± 13.4[c]	22.0 ± 4.97[c,c1]	98.3 ± 50.3[c1]

a, a1= p<0.001; b,b1= p<0.01; c,c1= p<0.05

Figure 1. Comparison of Total Protein, Albumin, Glucose and Creatinin Levels in Serum Samples among Groups
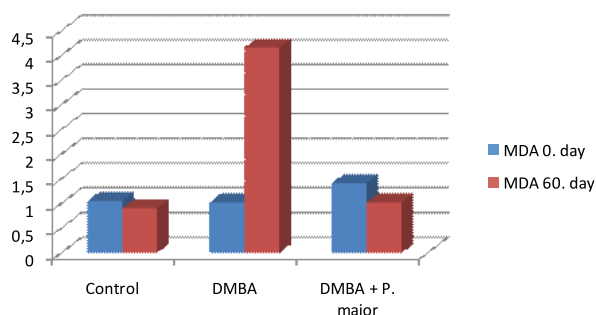
Figure 2. Comparison of MDA Levels in Whole Blood among Groups
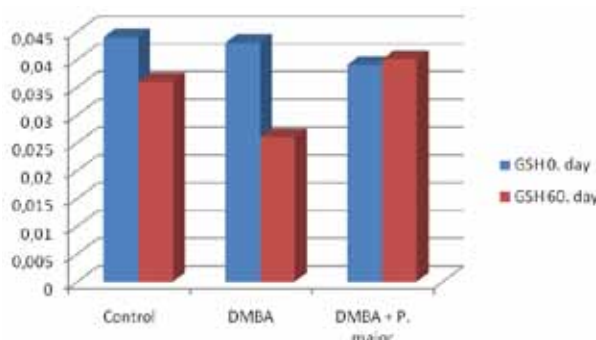
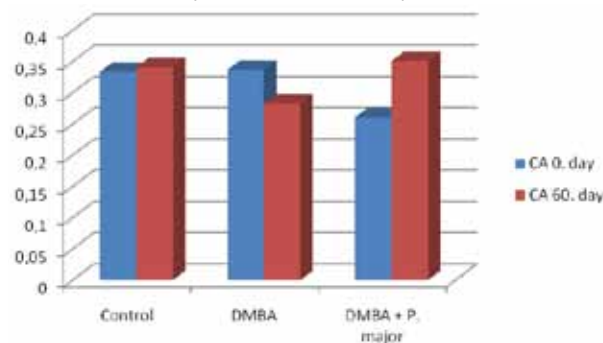**Figure 3. Comparison of GSH Levels in Whole Blood Samples among Groups**

in total protein (P<0.01) values in the DMBA group compared with the healthy controls and DMBA + Plantago major groups. Changes in albumin, glucose and creatinin values were not found statistically significant (p>0.05) as well (Table 1, Figure 1).

Levels of MDA and GSH
    O. Day data analyses showed that between the levels of parameters were not found statistically significant. After 60 days data analyses indicated a significant decrease in GSH (P<0.01) values in the DMBA group compared with the healthy controls and DMBA + Plantago major groups. However data analyses indicated a significant increase in MDA (P<0.01) values in the DMBA group compared with the healthy controls and DMBA + P. major groups (Table 1, Figure 2-3).

The activities of CA and CAT
    O. Day data analyses showed that between the levels of parameters were not found statistically significant for

Figure 4. Comparison of CA Activity in Erythrocytes among Groups
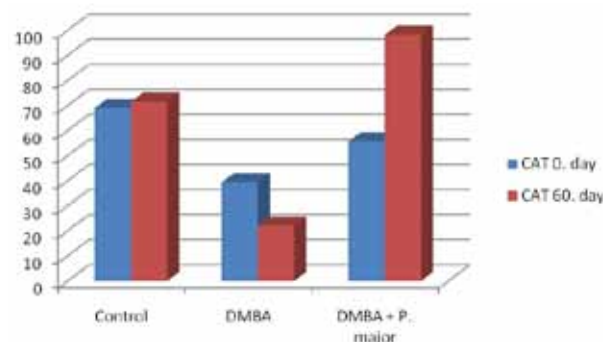
Figure 5. Comparison of CAT Activity in Erythrocytes among Groups

CAT. After 60 days data analyses indicated a significant decrease in catalase (P<0.05) and carbonic anhydrase (p≤0.01) values in the DMBA group compared with the healthy controls and DMBA + *Plantago major* groups (Table 1, Figure 4-5).

Discussion

The cellular systems may be the target for the toxicological effects of a wide variety of lipophilic chemical compounds such as PAH, if these compounds are not biotransformed to easily excretable hydrophilic metabolites (Rieder et al., 2000). DMBA treatments generate LPO and ROS in the affected area of organism and ultimately lead to carcinogenesis (Das et al., 2010). Antioxidant enzymes as well as antioxidant molecules protect the cells against oxidative stres (Burton et al., 1985). During oxidative stress, MDA and/or other aldehydes are formed in biological systems. These can react with aminoacids and DNA and introduce cross linkages between proteins and nucleic acids, resulting in alterations in replication, transcription (Perchellet and Perchellet, 1989) and tumor formation. Enhanced lipid peroxidation associated with antioxidant depletion in circulation is a characteristic findings in malignant transformation (Dreher and Junod, 1996). The increase in lipid peroxidation was associated with a decrease in the antioxidants (Frei et al.,1989). A decrease in the activities of CAT, CA and GSH, the major cellular detoxifying enzyme systems, has been reported in malignancies (Corrocher et al., 1986; Arivazhagan et al., 1997).
    The results of this study clearly demonstrates that carcinogen DMBA decreased the activities of antioxidant

enzymes (CAT, CA, GSH) and increased the lipid peroxidation (MDA) in rat. Similar parameters for other research has been reported previously (Lane and Modina, 1985; Bayoumy et al., 1992; Batcioglu et al., 2002) and our results are consistent with these findings. Plantago major leaf axtracts restore the loss of enzyme activities caused by DMBA treatment .

Glucose acts as a scavenger of hydroxyl radicals (Halliwel and Gutteridge, 1990). Muqbil and Banu (2006) shown that major antioxidants, glucose and albumin, were found to be decreased with increase in lipid peroxidation in serum of rats exposed to DMBA. In this study, changes in glucose, creatinin and albumin levels were not found significant differences between groups. After 60 days data analyses indicated a significant decrease in total protein levels in the DMBA group compared with the healthy controls and DMBA + Plantago major groups.

Plantago major is one of the most studied plants. Most of its components and the pharmacological action of some of them are well known (Velasco-Lezama et al., 2006). It is possible that acids known to be contained in the plant (caffeic, ferulic, chlorogenic, ursolic and oleanic acids), with proven antitumor activity in vitro (Liu, 1995) may have been destroyed and loose their cytotoxic and/or antitumor properties. Plantago major also major contains flavonoids namely, luteoline, apigenin, hispidulin, baicalein, etc., known for their capability of inducing carcinoma cell death (Matsuzaki et al., 1996). Galvez et al., (2003) reported that Plantago extracts have growth inhibitory and cytotoxic effects of breast adenocarcinoma and melanoma cell lines and these preliminary results could be justified by the cytotoxic activity of the flavone, luteolin-7-*O*-β-glucoside, the major flavonoid in Plantago species.

In this study, we have domonstrated that Plantago major provides protection for CAT, CA, MDA and GSH against oxidative stres and lipid peroxidation. We speculate that Plantago major mediates its chemopreventive effects by enhancing antioxidant status and decreasing lipid peroxidations . The results of the present study indicate that Plantago major may emerge as putative chemopreventive agents against DMBA toxicity.

Acknowledgments

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