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Effect of Cornus Mas l. Extract on Organs in Rats Given Nicotine

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Abstract: Nicotine plays an important role in oxidative stress formation. For this purpose, to reveal the antioxidant effect of cornelian cherry plant, the effects of nicotine-induced oxidative stress. 28 adult Wistar Albino (180-220 g) male rats were used in the study. Rats were divided into four groups as control group (n=6), cornelian cherry group (n=7), nicotine group (n=7) and nicotine+cornelian cherry group (n=8). While nicotine extract was applied to the experimental group, cornelian cherry extract was applied to the treatment group as well as nicotine. TBARS, SOD, GSH, GSSG, TOS, TAS, Redox potential values were measured by spectrophotometric analysis in lung, brain, kidney, heart and liver tissues. OSI and GSH/GSSG values were calculated as TOS/TAS and GSH/GSSG rates, respectively. When the experimental groups are examined, it is seen that there is a significant difference between the nicotine-treated group and the other groups ($p<0.05$). Its effects on lung, brain, kidney, heart and liver tissues are seen biochemically. Especially when the TAS value is examined, a significant difference is observed in the Nicotine group compared to other groups ($p<0.05$). Cornelian cherry is understood to be an important plant with antioxidant properties against nicotine by increasing TAS level against oxidative stress formation.

Keywords: Cornelian Cherry, Cornus Mas L., Nicotine, Oxidative Stress.

1. Introduction

Smoking is one of the biggest risk factors for the development of cancer, lung and cardiovascular diseases (1). Epidemiological studies have shown that smoking across the community is the most important risk factor for coronary heart disease and cardiovascular diseases (2). Smoking causes serious health problems by increasing the risk of thrombosis, atherosclerosis and death (3). In addition, the loss of productivity caused by it is considered as a public health problem (4).

There is usually 0.6-2 mg of nicotine in a single cigarette (5). Nicotine is one of the important chemicals in tobacco addiction (6). Tobacco consumption through smoking is known to promote a high level of free radical production in individuals. Free radicals oxidize proteins, lipids and DNA, leading to tissue damage (8). Exposure to cigarette smoke causes interleukins (IL-6) and myocardial inflammation in diabetes models through fibrosis, lipid peroxide and nitrite formation (9).

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Herbal extracts are widely used in complementary medicine (16). Cornelian cherry fruits are grown in some countries of Europe and West Asia (11). Fruits are usually dark or reddish, and sometimes pink and yellow. It is very beneficial nutritionally and is consumed as jam, liqueur and wine (10). *Cornus Mas L.* is rich in natural flavonoids, vitamins, phenolic acids and carotenes and is considered an antioxidant plant. It is also used in modern medicine as antimicrobial, anti-inflammatory, cardioprotective (12). Previous studies have shown that cornelian cherry plants have antioxidant and anti-carcinogenic effects (13).

Oxidative stress is one of the main causes of embryonal development disorders (15). Factors such as oxidative stress and inflammation are held responsible for the development of cardiovascular diseases (7). Oxidative stress is defined as an increase in oxidants or a decrease in functionally antioxidants. Therefore, antioxidant levels are important. In addition, oxidative stress plays an important role in cancer diseases and cancer's pathogenesis (13).

Total antioxidant status (TAS) is measured to determine overall antioxidant status. Total oxidant status is also measured (TOS). To assess the net oxidative stress in the organism, the oxidative stress index (OSI) is measured. OSI value is calculated by the ratio of TOS to TAS (13, 14).

Cornelian cherry (*Cornus mas L.*) belongs to the Umbelliferae Cornaceae family, is a type of fruit that sheds leaves in winter and can grow up to 7-8 meters (10). Turkey, many fruit species and different genotypes of these species has extremely important in terms of hosting ecology. *Cornus mas L.* is known as an herb with an effective antioxidant, antidiabetic and anti-inflammatory effects. Other studies have shown that *Cornus mas L.* is a powerful antioxidant and has an anti-carcinogenic effect (13).

2. Material and Methods

2.1. Experimental Design and Laboratory Animals Groups

28 adult Wistar Albino (180-220 g) male rats were included in the study. Rats were handled according to institutional guidelines and the Guide for Care and Use of Laboratory Animals of the National Research Council. The entire study was carried out according to 1986 Strasbourg Universal Declaration on Animal Welfare and was done with the approval of the ethics committee (2019 HADYEK-31). Free access to food and drinking water was provided for the compatibility of the animals to the laboratory 1 week before the experiment. Cages for animals' welfare were regularly ventilated and cleaned routinely. The animals were housed in a temperature control room (20-23 ºC) with a light/dark cycle of 12 hours throughout the experiment.

2.2. Experimental Groups

Control group (C) (n=6): During the experiment, 0.9% saline was applied once daily by subcutaneous (sc) injection.

Cornus Mas L. Group (CML) (n=7): 800 mg/kg *Cornus Mas L.* extract was given with gavage.

Nicotine group (N) (n=7): 4 mg/kg nicotine was given (sc).

Nicotine+Cornus Mas L. group (N+CML) (n=8): 4 mg/kg nicotine+800 mg/kg *Cornus Mas L.* extract was given.

These practices were carried out to all groups for 35 days.

2.3. Antioxidant indices and cytokines measurements

Activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and the levels of glutathione (GSH) and glutathione disulfide (GSSG) were measured in blood and tissue samples by the modified methods (20). Colorimetric kits were used to measure the levels of total anti-oxidative status (TAS), total oxidative status (TOS) and Thiobarbituric Acid Reactive Substances/malondialdehyde (TBARS/MDA). Each sample was analyzed in duplicate. Glutathione content was calculated using the formula GSH=T-GSH-(2×GSSG).The levels of GSH was calculated by the formula: GSH=GSHt-2×GSSG. The results of GSHt, GSH, and GSSG were normalized to the total protein content and were expressed as nmol of GSH or GSSG per mg of protein (nmol GSH/mg protein or nmol GSSG/mg protein). Oxidative stress index (OSI) value was calculated using the formula: OSI=[TOS (μmol H_2O_2 equiv./l)/TAS (μmol trolox equiv./l)×100]. Commercial enzyme-linked immunosorbent (ELISA) assay kits were used to measure the serum levels of cytokines (IL-6, TNF-α (Elabscience, MD, USA)).

2.4. Statistical Analysis

The statistical analysis on the obtained data was carried out on the computer using IBM SPSS 22.0 program. In the data obtained, 5 parameters were evaluated (kurtosis, skewness, mean-standard deviation ratio, Gauss curve, Shapiro-Wilko test and normal distribution analysis). Since all 5 parameters scored 3.5 and above, it was accepted that our data was normally distributed and parametric tests were applied. In statistical analysis, $\alpha=0.05$ was taken and $p<\alpha$ was considered statistically significant, while $p>\alpha$ was considered statistically insignificant.

3. Results

The results of biochemical analysis on oxidative stress parameters and antioxidant enzymes according to groups in lung, brain, kidney, heart, liver tissues taken from rats are given in the tables below.

When we examine the biochemical values, there is a significant difference in SOD, GPx, TAS, OSI, GSH/GSSG, Redox potential values between Nicotine+Cornus Mas L. group and other groups.
There is also a significant difference between the Nicotine group and other groups when looking at TBAS, SOD, GPx, TAS, OSI, GSH, GSSG, GSH/GSSG and Redox potential values. It is observed that lung tissue is biochemically affected in groups given nicotine (Table 1).

According to the results of biochemical analysis on brain tissue, TBARS, CAT, GPx, TAS, TOS, OSI and GSSG values of the Nicotine group had a statistically significant difference from other groups. TBARS values of Control, Cornus Mas L. and Nicotine+Cornus Mas L. groups were statistically similar, while TBARS of Nicotine group was significantly different from other groups.

Table 1. Cornelian cherry effect on lung tissue in groups given nicotine.

Parameters/Groups	C	CML	N	N+CML
TBARS	4.03±0.19^{a}	3.84±0.12^{a}	5.02±0.58^{b}	3.86±0.34^{a}
SOD	9.08±0.39^{a}	9±0.28^{a}	13.43±0.34^{b}	12.6±0.3^{c}
CAT	52.9±3.47^{a}	44.97±1.37^{b}	52.15±1.6^{a}	47±1.26^{b}
GPx	6.55±0.16^{a}	6.25±0.11^{a}	10.11±0.43^{b}	8.03±0.26^{c}
TAS	0.95±0.03^{a}	0.97±0.07^{a}	0.57±0.02^{b}	0.7±0.03^{c}
TOS	3.82±0.09^{a}	4.25±0.07^{a}	5.27±0.96^{b}	4.47±0.28^{a}
OSI	0.4±0.01^{a}	0.44±0.02^{a}	0.92±0.18^{b}	0.63±0.05^{c}
GSH	5.68±0.13^{a}	5.72±0.09^{a}	4.48±0.49^{b}	5.36±0.24^{a}
GSSG	0.87±0.05^{a}	0.85±0.01^{a}	1.52±0.24^{b}	0.99±0.13^{a}
GSH/GSSG	4.5±0.26^{a}	4.71±0.05^{a}	1.02±0.72^{b}	3.5±0.77^{c}
Redox potential	-71.01±0.28^{ac}	-71.53±0.22^{a}	-57.66±3.76^{b}	-67.95±2.34^{c}

P<0.05 was considered statistically significant. Data are expressed as Mean±Standard Deviation.The same letter indicates similarity between groups, different letters indicate differences between groups (C: Control group, CML: Cornus Mas L. group, N: Nicotin group, N+CML: Nicotine+Cornus Mas L. group).

Table 2. Cornelian cherry effect on brain tissue in groups given nicotine.

Parameters/Groups	C	CML	N	N+CML
TBARS	3.36±0.17^{a}	3.25±0.26^{a}	3.88±0.11^{b}	3.24±0.16^{a}
SOD	13.84±0.83^{a}	12.4±0.46^{b}	12.61±0.86^{b}	14.4±0.98^{a}
CAT	7.88±0.87^{a}	6.5±0.33^{b}	3.79±0.86^{c}	6.14±0.89^{b}
GPx	25.34±1.73^{ac}	24.38±0.32^{a}	31.45±1.34^{b}	26.07±1.4^{c}
TAS	1.02±0.05^{a}	1.05±0.07^{a}	0.49±0.03^{b}	0.96±0.06^{a}
TOS	7.19±0.92^{a}	7.19±0.33^{a}	11.49±1^{b}	9.08±0.24^{c}
OSI	0.7±0.11^{ac}	0.68±0.04^{a}	2.34±0.3^{b}	0.94±0.05^{c}
GSH	6.68±1.59^{a}	4.93±0.56^{b}	4.01±0.72^{b}	4.71±0.2^{b}
GSSG	0.4±0.04^{a}	0.4±0.01^{a}	0.61±0.03^{b}	0.53±0.06^{c}
GSH/GSSG	14.64±4.71^{a}	10.26±1.65^{b}	4.57±1.29^{b}	6.9±1.12^{b}
Redox potential	-84.56±7.31^{a}	-77.29±3.06^{b}	-66.27±4.78^{c}	-72.6±1.63^{bc}

P<0.05 was considered statistically significant. Data are expressed as Mean±Standard Deviation.The same letter indicates similarity between groups, different letters indicate differences between groups.

Table 3. Cornelian cherry effect on kidney tissue in groups given nicotine.

Parameters/Groups	C	CML	N	N+CML
TBARS	2.91±0.26^{a}	3.21±0.27^{a}	3.62±0.25^{b}	3.03±0.28^{a}
SOD	22.26±0.2^{a}	20.06±0.73^{b}	21.87±1.58^{ac}	20.44±1.27^{bc}
CAT	23.82±0.46^{a}	20.3±0.78^{a}	33.91±5.31^{b}	33.55±5.02^{b}
GPx	70.26±2.53^{a}	66.87±1.4^{a}	87.91±9.72^{b}	73±2.96^{a}
TAS	1.38±0.05^{a}	1.41±0.12^{a}	1.1±0.15^{b}	1.08±0.06^{b}
TOS	0.57±0.06^{a}	0.6±0.06^{ab}	0.69±0.11^{b}	0.7±0.05^{b}
OSI	0.04±0^{a}	0.04±0^{a}	0.06±0.01^{b}	0.06±0^{b}
GSH	5.14±0.99^{a}	3.88±0.19^{b}	4.36±0.74^{ab}	4.38±0.3^{ab}
GSSG	1.64±0.15^{a}	1.48±0.32^{a}	1.79±0.29^{a}	1.71±0.22^{a}
GSH/GSSG	1.15±0.78^{a}	0.71±0.48^{a}	0.45±0.38^{a}	0.57±0.23^{a}
Redox potential	-59.77±5.88^{a}	-54.46±2.20^{b}	-54.58±3.44^{ab}	-55.47±1.51^{ab}

P<0.05 was considered statistically significant. Data are expressed as Mean±Standard Deviation.The same letter indicates similarity between groups, different letters indicate differences between groups.

Table 4. Cornelian cherry effect on heart tissue in groups given nicotine.

Parameters/Groups	C	CML	N	N+CML
TBARS	2.89±0.19[a]	3.09±0.25[a]	3.63±0.24[b]	31±0.24[a]
SOD	15.5±0.49[a]	14.34±0.48[b]	17.13±0.84[c]	16.2±0.87[ac]
CAT	12.6±0.66[a]	10.8±0.36[a]	18.1±2.86[b]	16.12±3.11[b]
GPx	31.36±0.98[a]	30.07±0.54[a]	39.29±4.38[b]	32.78±1.34[a]
TAS	1.53±0.03[a]	1.57±0.12[a]	1.22±0.17[b]	1.2±0.07[b]
TOS	7.35±0.46[a]	9.08±0.68[b]	10.69±1.02[c]	9.19±0.9[b]
OSI	0.48±0.03[a]	0.57±0.04[b]	0.88±0.07[c]	0.76±0.06[d]
GSH	3.81±0.13[a]	3.21±0.53[ab]	2.49±0.8[b]	3.59±0.19[a]
GSSG	0.56±0.05[a]	0.5±0.1[a]	0.69±0.05[b]	0.58±0.08[ab]
GSH/GSSG	4.79±0.44[a]	4.73±1.96[a]	1.68±1.51[b]	4.28±0.9[a]
Redox potential	-66.38±0.47[a]	-63.3±6.24[a]	-51.66±8.32[b]	-64.48±2.58[a]

P<0.05 was considered statistically significant. Data are expressed as Mean±Standard Deviation.The same letter indicates similarity between groups, different letters indicate differences between groups.

Table 5. Cornelian cherry effect on liver tissue in groups given nicotine.

Parameters/Groups	C	CML	N	N+CML
TBARS	3.07±0.13[a]	3.62±0.25[b]	4.2±0.2[c]	3.73±0.18[b]
SOD	20.77±0.15[a]	18.32±0.68[b]	14.78±0.72[c]	19.95±0.55[a]
CAT	25.19±0.29[a]	21.49±0.83[b]	11.34±0.99[c]	21.53±0.85[b]
GPx	21.06±0.65[a]	20.15±0.46[a]	20.1±1.69 [a]	19.64±0.8 [a]
TAS	1.46±0.01[a]	1.5±0.12[a]	0.51±0.07[b]	0.94±0.18[c]
TOS	8.79±0.67[a]	8.12±1.51[a]	14.84±2.46[b]	13.22±0.54[b]
OSI	0.59±0.05[a]	0.54±0.1[a]	2.94±0.7[b]	1.43±0.21[c]
GSH	10.33±0.53[a]	8.95±1.53[a]	7.02±1.04[b]	9±0.33[a]
GSSG	2.51±0.13[a]	2.29±0.5[a]	3.13±0.33[b]	2.41±0.15[a]
GSH/GSSG	2.11±0.31[a]	2.1±1.19[a]	0.29±0.6[b]	1.74±0.37[a]
Redox potential	-72.82±1.6[a]	-70.21±6.27[a]	-59.73±5.14[b]	-69.76±1.68[a]

P<0.05 was considered statistically significant. Data are expressed as Mean±Standard Deviation.The same letter indicates similarity between groups, different letters indicate differences between groups.

There was no significant difference in GSH, GSH/GSSG and Redox potential biochemical values in the brain dox between the Nicotine group and the Nicotine+Cornus Mas L. group (Table 2).

When kidney tissue was examined, there was a significant difference between the Nicotine group and other groups in terms of TBARS and GPx values. There was no statistically significant difference in SOD, CAT, TAS, TOS, OSI, GSH, GSSG, GSH/GSSG and Redox potential values between the Nicotine group and the Nicotine+Cornus Mas L group. The effect of cornelian cherry plant on the specified biochemical values in kidney tissue has not been observed (Table 3).

In heart tissue biochemical analysis, the TBARS, GPx, TOS, OSI, GSH/GSSG and Redox potential values of the Nicotine group were statistically different compared to the other groups. There is a significant difference between the Nicotine group and the Nicotine+Cornus Mas L group in TBARS, GPx, TOS, OSI, GSH, GSH/GSSG and Redox potential values (Table 4).

Except for the GPx and TOS values of the nicotine group, all values have a statistically significant difference from those of the other groups. As a result of the data obtained, the negative effect of nicotine on liver tissue is clearly seen (Table 5).

GPx (Glutathione peroxidase) is an antioxidant enzyme localized in the cytosol and mitochondria matrix. In our study, GPx level in kidney, lung, brain and heart had a significant difference between nicotine group and other groups.

4. Discussion

Nicotine is an important toxic component of cigarette smoke, has devastating and malignant consequences (19). Smoking is among the most important risk factors for diseases such as coronary diseases, chronic obstructive pulmonary disease and lung cancer.

Since the lung is the main organ exposed to cigarette smoke and is the main region of nicotine absorption, it has been accepted as a highly sensitive organ against the toxic effect and free radical formation of nicotine (20).

It is known that antioxidants taken from plants contribute to the defense system against oxidative stress. Thus, they can protect cells against oxidative damage and prevent chronic diseases (22).

The decrease in antioxidant enzyme activities (SOD, CAT and GPx) and increase in peroxidation reactions in the liver show oxidative stress in animals exposed to nicotine (23). To reduce the toxicity of nicotine, cellular antioxidant enzymes are produced for defense purposes. Thus, inhibition of enzymes, lipid peroxidation and gene expression in rats exposed to nicotine changes and leads to cell death (25).

In our study, it was investigated whether nicotine in rats caused biochemical changes on heart, brain, liver, kidney and lung tissue and whether cornelian cherry plant had any role in response to this effect. Seher et al., in their study, they investigated the effect of cornelian cherry plant in mice with ehrlich solid tumor and reached the conclusion that TAS, GSH and SOD values were lower in all tissues of the tumor group compared to the control group (13). The plant extract (curcumin 50 mg/kg) used in the study by Mustafa et al., appears to increase CAT activity in the kidney (17).

The SOD enzyme is found in excessive amounts in the liver, adrenal gland, kidney, spleen and erythrocytes, where oxygen pressure is high (18). Therefore, in our study, we examined SOD values in kidney and liver. SOD value in liver was lower in nicotine group compared to other groups and there was a significant difference between other groups. In kidney, SOD value was significantly lower in nicotine group compared to control group. In study by Dhouib et al. there is an increase in CAT and SOD values in the lung tissue in the group given nicotine (21). It shows similar results with our study.

In another study, Karafakioğlu et al. stated that there was a significant decrease in erythrocyte levels compared to the control group and that erythrocytes were vulnerable to oxidative stress (26). In their study on diabetic rats, Karabulut et al. stated that myocardial damage due to oxidative stress was caused by insufficient reactive oxygen production (27). In our study, the TBARS level in the heart tissue of the group given nicotine was calculated as 3.63±0.24. Accordingly, nicotine appears to cause oxidative stress in the heart. In another study, it was observed that oxidative stress decreased antioxidant enzyme activities in liver damage caused by Lipopolysaccharide (LPS) (28). In our study, it is seen that SOD and CAT decreased in nicotine group compared to other groups, and increased TBARS value. Thus, nicotine appears to increase oxidative stress in the liver.

Oxidative stress is an important phenomenon expressed by excessive accumulation of TBARS (24). In our study, 5.02±0.58 in TBARS lung tissue in nicotine group; 4.2±0.2 in liver tissue; 3.63±0.24 in the heart; 3.62±0.25 in kidney; and it was found to be 3.88±0.11 in the brain. Thus, the high TBARS values of nicotine groups indicate that nicotine causes oxidative stress in the organs we specify.

5. Conclusions

Oxidative stress caused by nicotine was created in rats and antioxidant properties of cornelian cherry extract were evaluated. According to the results, cornelian cherry plant has an antioxidant feature against nicotine. Based on these data, cranberries can be considered as an alternative medicinal plant for tobacco users and other conditions that cause oxidative stress.

Conflict of interest statement

There is no conflict of interest.

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