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Serhet Keser
Ökkeş Yılmaz
Mehmet Tuzcu
Firat University
serhatkeser@gmail.com
Elazig-Turkey

THE EFFECTS OF RESVERATROL AND POTASSIUM BROMATE ON FATTY ACID LEVELS IN LUNG, LIVER AND KIDNEY OF WISTAR RATS

ABSTRACT

Resveratrol is a polyphenolic compound found in grapes and wine, have anti-oxidant and anti-tumor activities. The aim of this research was to examine the effects of resveratrol and potassium bromate on the level of fatty acids in lung, liver and kidney of Wistar rats. According to our results, in the lung, stearic acid (18:0) level was increased in the R group. Arachidonic acid (20:4) and saturated fatty acids levels were increased in the K and R group. In the liver, stearic acid (18:0) level was increased in the K and R groups. Arachidonic acid (20:4) level was increased in the R group. In the kidney, palmitic acid (16:0), oleic acid (18:1), linoleic acid (18:2), linolenic acid (18:3 n-3), eicosenoic acid (20:1) levels were decreased in the K and R groups when compared to C group. On the other hand, stearic acid (18:0), arachidonic acid (20:4), docosapentaenoic acid (22:5), docosahexaenaoic acid (22:6) and lignoseric acid (24:0) levels were increased in the K and R groups when compared to C group. Our results indicate that the applications of $KBrO_3$ and resveratrol influenced fatty acid levels, and this application was affected that the amount of important fatty acids which substrates in fatty acids metabolism on duty enzymes.

Keywords: Resveratrol, Potassium Bromate, Lung, Kidney, Liver, Stearic Acid

WİSTAR SIÇANLARIN AKCİĞER, KARACİĞER VE BÖBREK DOKULARINDAKİ YAĞ ASİDİ DÜZEYİNE RESVERATROL VE POTASYUM BROMATIN ETKİLERİ

ÖZET

Resveratrol, antioksidan ve antitümör özelliklere sahip, üzümde ve şarapta bulunan polifenolik bir bileşiktir. Bu araştırmanın amacı, resveratrol ve potasyum bromatın Wistar ratların akciğer, karaciğer ve böbrek dokularında yağ asidi düzeyine etkisini incelemektir. Sonuçlarımıza göre, akciğer dokusunda, stearik asit (18:0) miktarı R grubunda; araşidonik asit (20:4) ve doymuş yağ asitleri miktarı K ile R gruplarında azalmıştır. Karaciğer dokusunda, stearik asit K ve R gruplarında artarken; araşidonik asit (20:4) ise R grubunda artmıştır. Böbrek dokusunda, palmitik asit (16:0), oleik asit (18:1), linoleik asit (18:2), linolenik asit (18:3 n-3) ve eikosenoik asit (20:1) düzeyleri C grubuyla karşılaştırıldığında K ve R gruplarında azaldığı saptanmıştır. Öte yandan stearik asit (18:0), araşidonik asit (20:4), dokosapentaenoik asit (22:5), dokosahekzaenoik asit (22:6) ve lignoserik asit (24:0) düzeyleri, C grubuyla karşılaştırıldığı zaman K ve R gruplarında arttığı görülmüştür. Sonuçlarımız göstermiştir ki, resveratrol ve $KBrO_3$ uygulaması yağ asidi seviyelerini etkilemiştir ve bu uygulama yağ asidi metabolizmasında görevli enzimlerin substratları olan bazı önemli yağ asitlerinin miktarlarını etkilemiştir.

Anahtar Kelimeler: Resveratrol, Potasyum Bromat, Akciğer, Böbrek, Karaciğer, Stearik Asit

1. INTRODUCTION (GİRİŞ)

The interest of the scientific community in the phytoalexin resveratrol has increased over the last years. The interest was originally sparked by epidemiological studies, indicating an inverse relationship between moderate wine consumption and risk of coronary heart disease, the so called "French Paradox" [1] and by the fact that cancer preventive properties of resveratrol was observed *in vitro* and *in vivo* [2].

Resveratrol (3,4′,5-trihydroxystilbene) is a natural phytoalexin synthesized in a wide variety of plant species including grapes as a response to environmental stress or fungal infection. It constitutes one of the polyphenolic compounds of red wine and is responsible for the beneficial effect of regular wine consumption at moderate amounts [3]. The positive effects of resveratrol in biological systems are wide-ranging as a cancer chemoprevention agent [4], a powerful anti-inflammatory factor [5] and an antioxidant agent [6]. Several investigations have cited the possible role and protective effects of resveratrol against certain forms of oxidant damage, through a hydrogen-electron donation from its hydroxyl groups [7].

Resveratrol is a polyphenol present in a variety of plant species, used for human consumption, e.g., peanuts, berries and grapes. The highest levels of naturally occurring resveratrol is found in the roots of Japanese Knotweed (*Polygonum cuspidatum*), which has been used in traditional Asian herb medicine for hundreds of years to treat inflammation [8]. Grapes are probably the most important source of resveratrol for humans, since the compound is also found in one of the end products of grapes, i.e., wine [9]. Resveratrol is found in white, rose and red wines, but as the highest amount of resveratrol are found in red wines [10], the present review focus on these wines.

Potassium bromate ($KBrO_3$) is one compound which is used as an oxidizing agent for the treatment of wheat flour and small amounts may be consumed by humans. Although there is no epidemiological data to suggest conclusively that $KBrO_3$ is a human carcinogen, it has been shown to produce ROS [11], lipid peroxidation [12] and 8-hydroxyguanosine (8-OH-dG) modification in kidney DNA [13]. Long term exposure of this compound leads to the induction of renal cell tumors in both male and female F344 rats [14]. Its consumption has also been shown to enhance N-ethyl-hydroxyethyl-nitrosamine initiated renal tumors in rats [15]. Recently, it has been shown that $KBrO_3$-mediated generation of oxidative stress may lead to an enhancement in cellular proliferation in kidney [16]. However, detailed studies showing the effect of $KBrO_3$ on antioxidant armoury and development of oxidative stress leading to the induction of biochemical responses implicated in cellular proliferation and tumor promotion are lacking.

With a single dose of $KBrO_3$ (80 mg/kg), activity in the kidney was found to increase significantly at 3 h in comparison to that at zero time [17]. $KBrO_3$ is carcinogenic in the rat kidney, thyroid, and mesothelium and is a renal carcinogen in male mice [18, 19].

Fatty acids are used as major substrates for the synthesis of various kinds of lipid including phospholipids, triacylglycerol and cholesterol esters. Oleate is the most abundant monounsaturated fatty acid found in triacylglycerol, cholesterol esters, wax esters and phospholipids [20]. The ratio of stearic acid to oleic acid has been implicated in the regulation of cell growth and differentiation through effects on membrane fluidity and signal transduction [21]. Monounsaturated fatty acids also influence apoptosis and may have some role in mutagenesis of some tumors [22].

Polyunsaturated and monounsaturated fatty acids are important for normal growth, development and are suggested to play an important role in modulation of cardiovascular inflammatory diseases and cancer [23, 24]. The variable health effects may be produced by n-3 and n-6 fatty acids themselves, which serve as structural components of membrane phospholipids.

Their products modulate the biosynthesis of potent cellular mediators, eicosanoids [25].

2. RESEARCH SIGNIFICANCE (ÇALIŞMANIN ÖNEMİ)

The aim of this study was to examine effects of resveratrol and kidney carcinogen potassium bromate on the level of fatty acids in lung, liver and kidney tissue of Wistar albino rats.

3. EXPERIMENTAL METHOD-PROCESS (DENEYSEL ÇALIŞMA)

3.1. Animals (Hayvanlar)

In this study, a total 30 old female Wistar rats were used. They were housed in cages where they had *ad libitum* rat chow and water in an air-conditioned room with a 12-h light/12-h dark cycle, and were randomly divided into three groups. The first group was used as a control, the second group potassium bromate ($KBrO_3$), and third group R+$KBrO_3$. Rats in the $KBrO_3$ and R+$KBrO_3$ groups were injected intraperitoneally a single dose potassium bromate 0.48 mM/kg in physiologic saline buffer. After administration of $KBrO_3$ two days, the rats in R+$KBrO_3$ group was injected resveratrol 0.15 mM/kg four times per week. In addition, in control group rat's physiological saline were injected. These treatments were continued for five weeks, after which time each experimental rat was decapitate and blood samples were collected and stored in -85 °C prior to biochemical analysis.

3.2. Lipid Extraction (Lipitlerin Ekstraksiyonu)

Total lipids were extracted with hexane-isopropanol (3:2 v/v) by the method of Hara and Radin [26]. The tissue samples were homogenized. 200 mg lung, 500 mg liver and 400 mg kidney of the homogenized tissue samples were taken and mixed with 5 ml hexane-isopropanol (3:2, v/v) in a mixer. Non-lipid contaminants in lipid extracts were extracted into 0.88% KCl solution.

3.3. Fatty Acid Analysis (Yağ Asidi Analizi)

Fatty acids in the lipid extracts were converted into methyl esters including 2% sulphuric acid (v/v) in methanol [27]. The fatty acid methyl esters were extracted three times with n-hexane. Then the methyl esters were separated and quantified by gas chromatography and flame-ionization detection (Shimadzu GC 17 Ver.3) coupled to a Glass GC 1.0 software computing recorder. Chromatography was performed with a capillary column (25m in length) and 0.25mm in diameter, Permabound 25, Machery-Nagel, Germany using nitrogen as a carrier gas (flow rate 0.8 ml/min). The temperatures of the column, detector and injection valve were 130-220, 240, 280 °C, respectively. Identification of the individual methyl esters was performed by frequent comparison with authentic standard mixtures that were analyzed under the same conditions.

3.4. Statistical Analysis (İstatistiksel Analiz)

The experimental results were reported as mean ± S.E.M. Statistical analysis was performed using SPSS statistical software. Analysis of variance (ANOVA) and an LSD test was used to compare the experimental groups with the controls.

4. FINDINGS AND DISCUSSIONS (BULGULAR VE TARTIŞMALAR)

In this study, the levels of fatty acids in the lung, liver and kidney of old female Wistar rats by induced kidney carcinogen potassium bromate were examined.

- **The Fatty Acid Composition of Lung:** The fatty acid composition of lung is shown at Table 1. Palmitic acid (16:0) and palmitoleic acid (16:1) levels were increased in the K group when compared to C group

(p<0.05). Stearic acid (18:0) level was increased in the R group (p<0.05). Oleic acid (18:1) and monounsaturated fatty acids (MUFA) levels were decreased in the R group (p<0.05, p<0.01, respectively). Linoleic acid (18:2), lignoceric acid (24:0) and unsaturated fatty acids levels were decreased in the K and R group when compared to C group (p<0.01, p<0.05, p<0.01, respectively). Arachidonic acid (20:4) and saturated fatty acids levels were increased in the K and R group (p<0.05). Polyunsaturated fatty acids (PUFA) and n-6 fatty acids levels were decreased in the K group (p<0.01, p<0.05, respectively). While the level of eicosatrienoic acid (20:3) was decreased in the K group, its level was increased in the R group when compared to C group (p<0.05, p<0.01, respectively).

Table 1. The fatty acid composition of lung lipids (%)
(Tablo 1. Akciğer yağlarının yağ asidi kompozisyonu) (%)

Fatty Acids	Control (C)	$KBrO_3$ (K)	$KBrO_3$+R (R)
16:0	30.54±1.09^a	32.79±0.56^b	31.44±0.40^a
16:1 n-7	5.13±0.51^a	6.33±0.34^b	4.92±0.25^a
18:0	9.33±0.92^a	9.62±0.21^a	10.88±0.29^b
18:1 n-9	21.29±0.48^a	20.08±0.76^a	19.31±0.34^b
18:2 n-6	14.46±0.51^a	11.21±0.52^c	12.25±0.54^b
20:3 n-6	0.43±0.04^a	0.32±0.10^b	0.62±0.06^c
20:4 n-6	7.27±0.13^a	9.81±0.41^b	9.09±0.55^b
22:0	0.61±0.03^a	0.71±0.03^a	0.63±0.02^a
22:4	0.37±0.03^a	0.33±0.05^a	0.40±0.05^a
22:5 n-6	1.14±0.07^a	1.48±0.13^a	1.42±0.05^a
22:5 n-3	1.61±0.20^a	1.80±0.11^a	1.94±0.13^a
22:6 n-3	3.72±0.41^a	4.17±0.31^a	4.01±0.37^a
24:0	0.83±0.03^a	0.58±0.05^b	0.59±0.07^b
∑Saturated	43.94±1.86^a	46.13±0.56^b	45.05±0.92^b
∑Unsaturated	58.66±0.81^a	53.68±1.40^c	54.15±1.03^c
∑MUFA	27.77±1.14^a	27.28±1.47^a	24.53±0.83^c
∑PUFA	30.88±0.79^a	27.57±2.46^c	31.07±1.44^a
∑n-3	6.87±0.68^a	6.30±0.76^a	7.11±0.57^a
∑n-6	23.87±0.64^a	21.08±1.78^b	24.09±1.02^a

a: p>0.05 **b:** p<0.05 **c:** p<0.01 **d:** p<0.001

- **The Fatty Acid Composition of Liver:** The fatty acid composition of liver is shown at Table 2. Palmitic acid (16:0) level was decreased in the K and R groups when compared to C group (p<0.05). Stearic acid (18:0) level was increased in the K and R groups (p<0.05). Linoleic acid (18:2) and linolenic acid (18:3) levels were decreased in the R group (p<0.05). Arachidonic acid (20:4) level was increased in the R group (p<0.05). Unsaturated fatty acids and MUFA levels were increased in the K group when compared to C group (p<0.05).

Table 2. The fatty acid composition of liver lipids (%)
(Tablo 2. Karaciğer yağlarının yağ asidi kompozisyonu) (%)

Fatty Acids	Control (C)	$KBrO_3$ (K)	$KBrO_3$+R (R)
16:0	20.00±0.45^a	17.85±0.30^b	17.92±0.42^b
16:1 n-7	2.22±0.13^a	2.32±0.10^a	2.19±0.16^a
18:0	20.92±0.61^a	23.23±0.15^b	22.71±0.25^b
18:1 n-9	5.28±0.13^a	4.85±0.47^a	5.04±0.24^a
18:2 n-6	17.45±0.14^a	17.62±0.49^a	15.76±0.39^b
18:3 n-6	0.15±0.01^a	0.16±0.01^a	0.19±0.01^a
18:3 n-3	0.35±0.02^a	0.26±0.02^a	0.19±0.02^b
20:2 n-6	0.25±0.01^a	0.27±0.01^a	0.27±0.02^a
20:3 n-6	0.96±0.11^a	1.05±0.06^a	1.11±0.05^a
20:4 n-6	14.00±0.29^a	14.59±0.85^a	16.24±0.30^b
20:5 n-3	3.51±0.12^a	3.62±0.46^a	3.04±0.23^a
22:4	0.34±0.03^a	0.30±0.02^a	0.32±0.02^a
22:5 n-6	0.12±0.01^a	0.12±0.01^a	0.14±0.01^a
22:5 n-3	1.14±0.04^a	0.96±0.05^a	0.99±0.03^a
22:6 n-3	11.64±0.30^a	11.47±0.32^a	11.99±0.27^a
∑Saturated	42.57±0.34^a	41.27±0.23^a	41.89±0.67^a
∑Unsaturated	57.58±0.34^a	59.61±0.23^b	58.25±0.67^a
∑MUFA	11.20±0.27^a	12.62±1.53^b	11.08±0.44^a
∑PUFA	46.43±0.24^a	46.95±1.52^a	47.33±0.41^a
∑n-3	16.36±0.22^a	15.69±0.97^a	16.23±0.35^a
∑n-6	29.65±0.36^a	30.54±0.51^a	30.76±0.54^a

a: $p>0.05$ **b:** $p<0.05$ **c:** $p<0.01$ **d:** $p<0.001$

- **The Fatty Acid Composition of Kidney:** The fatty acid composition of kidney is shown at Table 3. Palmitic acid (16:0), oleic acid (18:1), linoleic acid (18:2), linolenic acid (18:3 n-3), eicosenoic acid (20:1) levels were decreased in the K and R groups when compared to C group ($p<0.01$, $p<0.001$, $p<0.001$, $p<0.05$, $p<0.05$, respectively). Stearic acid (18:0), linolenic acid (18:3 n-6), eicosadienoic acid (20:2), eicosatrienoic acid (20:3), arachidonic acid (20:4), eicosapentaenoic acid (20:5), docosadienoic acid (22:2), docosapentaenoic acid (22:5), docosahexaenaoic acid (22:6) and lignoseric acid (24:0) levels were increased in the K and R groups when compared to C group ($p<0.01$, $p<0.05$, $p<0.05$, $p<0.05$, $p<0.001$, $p<0.05$, $p<0.05$, $p<0.05$ $p<0.05$ $p<0.01$, respectively). Unsaturated fatty acids and MUFA levels were decreased in the K group ($p<0.01$). PUFA and n-3 fatty acids levels were increased in the R group ($p<0.01$, $p<0.05$, respectively).

Table 3. The fatty acid composition of kidney lipids (%)
(Tablo 3. Böbrek yağlarının yağ asidi kompozisyonu) (%)

Fatty Acids	Control (C)	$KBrO_3$ (K)	$KBrO_3$+R (R)
16:0	26.13±0.36^a	24.32±1.03^b	23.33±0.39^c
16:1 n-7	5.21±0.35^a	5.06±0.84^a	4.85±0.17^a
18:0	6.42±0.57^a	9.31±1.50^c	10.26±1.07^c
18:1 n-9	24.04±1.14^a	18.23±1.56^d	19.86±1.26^c
18:2 n-6	20.47±0.64^a	17.25±0.58^c	15.65±0.43^d
18:3 n-6	0.17±0.02^a	0.32±0.04^b	0.31±0.03^b
18:3 n-3	0.81±0.06^a	0.56±0.10^b	0.48±0.06^b
20:1 n-11	0.62±0.05^a	0.39±0.03^b	0.40±0.03^b
20:1	0.32±0.04^a	0.14±0.03^b	0.17±0.02^b
20:2	0.31±0.02^a	0.48±0.06^b	0.45±0.05^b
20:3 n-6	0.38±0.05^a	0.73±0.11^b	0.71±0.05^b
20:4 n-6	5.51±1.02^a	11.53±1.19^c	12.80±1.68^d
20:5 n-3	0.66±0.12^a	1.14±0.11^b	1.00±0.10^b
22:2	0.20±0.05^a	0.33±0.05^b	0.35±0.01^b
22:4	0.58±0.08^a	0.52±0.08^a	0.50±0.04^a
22:5 n-6	0.20±0.03^a	0.31±0.02^b	0.32±0.02^b
22:5 n-3	0.44±0.03^a	0.47±0.04^a	0.44±0.03^a
22:6 n-3	2.25±0.28^a	3.16±0.41^b	3.48±0.18^b
24:0	0.23±0.04^a	0.38±0.09^b	0.43±0.02^c
∑Saturated	35.08±0.80^a	36.09±0.53^a	35.79±0.81^a
∑Unsaturated	66.68±1.11^a	62.08±0.98^c	66.68±0.77^a
∑MUFA	32.26±1.17^a	28.04±2.25^c	30.11±1.60^a
∑PUFA	32.41±1.24^a	33.97±2.28^a	36.60±1.62^c
∑n-3	27.34±0.75^a	27.82±1.81^a	30.32±1.38^b
∑n-6	4.17±0.39^a	5.35±0.44^a	5.40±0.21^a

a: $p>0.05$ **b:** $p<0.05$ **c:** $p<0.01$ **d:** $p<0.001$

Experimental studies have pointed beneficial effects of resveratrol compound such as, improvement of lipid profile and lipoprotein metabolism [28, 29], antioxidant activity [30-32].

According to our results belong to the lung tissue, 16:0 fatty acid level was increased in the K group. In addition, in the lung tissue while 18:0 fatty acid level was increased in the R group, 18:1 level was decreased in same group when in comparison to C group (Table 1). Similarly, the increasing of 18:0 and the decreasing of 18:1 values in the R group can be explained by the decreasing of Stearoyl-CoA desaturase (SCD) enzyme activity. The desaturating enzymes, Δ^9-desaturase (also referred to as stearoyl-CoA-desaturase (SCD)), Δ^6-desaturase (Δ^6D) and Δ^5-desaturase (Δ^5D), introduce cis-double bonds in the carbon chain of long chain fatty acids [33]. These enzymes catalyze the synthesis of the long chain monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), which are needed to maintain membrane structures, to participate in cellular communication and differentiation, for eicosanoid signaling and to regulate gene expression [33,21]. SCD is an endoplasmic reticulum enzyme that catalyzes the biosynthesis of monounsaturated fatty acid from saturated fatty acids, and it is a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids. SCD expression affects the fatty acid composition of membrane phospholipids, triacylglycerol and cholesterol esters, resulting in changes in membrane fluidity, lipid metabolism and obesity [33]. SCD can convert the 18:0 fatty acids to the 18:1 fatty acids [34,35]. Therefore, the levels of MUFA were decreased in the R group of the

lung tissue. These results indicated that the administrations of resveratrol and potassium bromate were affected the activities of enzymes in fatty acids metabolism and this result is harmonious with enzyme activities. In the lung, the levels of PUFA and n-6 fatty acids were decreased in the K group. Lipids, especially PUFA are preferential targets of oxidative damage [36]. *In vitro* experiments have shown that the more double bonds a polyunsaturated fatty acid has, the more vulnerable to peroxidation it is [37]. This event was indicated that the administration of potassium bromate caused to these fatty acids oxidations and their levels were decreased in this group. Formerly studies were put forwarded that potassium bromate an oxidizing agent [38]. The level of 20:4 increased in the K and R groups when in comparison to C group ($p<0.05$). This event has shown that the administration of potassium bromate may be affected Δ^6 desaturation pathway synthesis. This metabolic even is catalyze by $\Delta^{5,6}$ desaturase enzymes and it investigate in essential fatty acid metabolism. Because, increasing of the level of 20:4 can be explained by increasing of the activities of desaturase enzymes. The 20:4 is an important fatty acid that found in cellular membrane phospholipids, and it is the release by arachidonyl-hydrolyzing phospholipase A_2 (PLA_2) enzyme [39-41].

According to our results of the liver tissue, while 16:0 fatty acid level was decreased in the K and R groups, 18:0 level fatty acid level was increased in the same groups when comparison to C group (Table 2). The increasing of 18:0 in the K and R groups can be explained by the decreasing of SCD enzyme activity [34,35].

In the present study, 16:0 fatty acid level was decreased in the K and R groups when comparison to C group in the kidney tissue (Table 3). While 18:0 fatty acid level was increased in the K and R groups, 18:1 and 18:2 fatty acid levels were decreased in the same groups. According to these results, the increasing of 18:0 and the decreasing of 18:1 in the K and R groups can be explained by the decreasing of Stearoyl-CoA desaturase (SCD) enzyme activity. [33]. There are the multiple roles of monounsaturated fatty acids, variation in SCD activity in mammals would be expected to affect a variety of the key physiological variables, including differentiation, insulin sensitivity, metabolic rate, adiposity, atherosclerosis, cancer and obesity [21].

We have not found any study about the effect of potassium bromate on fatty acids.

5. CONCLUSION AND RECOMMENDATIONS (SONUÇ VE ÖNERİLER)

Our results showed that the application of potassium bromate and resveratrol can be affected to the amounts of important fatty acids that the substrates of fatty acid metabolism on duty enzymes in the lung, liver and kidney. However, more investigations are required to evaluate the effects of resveratrol and potassium bromate on the fatty acids in the experimental models.

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