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Investigation of Antioxidant/Oxidant Potential of Some Natural Biomaterials

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Research Article

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Abstract

Recent studies have focused on plant-based antioxidative materials and biomaterials that serve as remedies or preventive agents against oxidative stress-induced damage in organisms. Various methods exist to evaluate the antioxidant potential of these compounds. Antioxidants neutralize free radicals in biological cells, mitigating their harmful effects on living organisms. This study aimed to investigate the *in vivo* protective effects of naringin, silymarin and ellagic acid which are known to contribute to tissue repair following short-term ischemia/reperfusion (I/R) injury. Three-week-old, clinically healthy, Wistar albino rats (n: 35), weighing 250-300 g, were used in this study. Blood samples were analyzed for plasma paraoxonase (PON), total sialic acid (TSA), total antioxidant capacity (TAC) and total oxidant capacity (TOC), oxidative stress index (OSI) and nitric oxide (NO) levels. Results demonstrated that TSA, TOC and NO levels decreased while TAC and PON levels increased following biomaterial administration ($P<0.05$). This study confirmed that silymarin, naringin and ellagic acid exhibit free radical scavenging, anti-inflammatory, radioprotective, antiulcerogenic, and analgesic properties. Given the obtained *in vivo* results, we conclude that, they might be considered as promising candidates to reduce the effects and the levels of oxidative stress during *in vivo* and *in vitro* applications.

Keywords: Free radical, ischemia/reperfusion, nitric oxide, total antioxidant/oxidant capacity

Bazı Doğal Biyomateryallerin Antioksidan/Oksidan Potansiyelinin Araştırılması

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Öz

Son zamanlarda yapılan çalışmaların çoğu, organizmada oksidatif stresin oluşturduğu zararlara çare veya önleyici olarak görev yapan bitki bazlı antioksidatif materyaller ve biyomateryaller üzerine yoğunlaşmıştır. Antioksidanların potansiyel düzeyini değerlendirmek için çeşitli yollar sağlayan farklı yöntemler vardır. Antioksidanlar, biyolojik hücrelerde bulunan ve canlı organizmalar üzerinde olumsuz etkiye sahip olan serbest radikalleri nötralize etmektedir. Bu çalışmanın amacı, kısa süreli iskemi/reperfüzyon (I/R) ile ortaya çıkan hasarlı dokuyu tedavi eden biyomateryaller olarak bilinen naringin, silymarin ve ellagik asitlerin potansiyel koruyucu etkilerinin *in vivo* olarak incelenmesidir. Bu çalışmada, 3 haftalık, klinik olarak sağlıklı, 250-300 g ağırlığında Wistar albino rat (n: 35) kullanıldı. Sıçanlardan alınan kan örneklerinde Plazma Paraoksonaz (PON), toplam sialik asit (TSA), toplam antioksidan kapasite (TAK) ve toplam oksidan kapasite (TOK), oksidatif stres indeksi (OSI) ve Nitrik Oksit (NO) analiz edildi. Sonuçlar, biyomateryal kullanımından

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sonra TSA, TOK ve NO düzeylerinin azaldığını, TAK ve PON düzeylerinin ise arttığını ortaya koymaktadır (P<0.05). Bu çalışma aynı zamanda silymarin, naringin ve ellagik asitlerin serbest radikal temizleyici, antiinflamatuar, radyoprotektif, antiülserojenik, analjezik ve antikarsinojenik özelliklerinin varlığını da doğruladı. Elde edilen *in vivo* sonuçlar göz önüne alındığında, *in vivo* ve *in vitro* uygulamalarda oksidatif stresin etkilerini ve düzeyini azaltmak için umut verici bir aday olarak değerlendirilebilecekleri sonucuna varılmıştır.

Anahtar Kelimeler: Serbest radikal, iskemi/reperfüzyon, nitrik oksit, toplam antioksidan/oksidan kapasite

Introduction

Reperfusion is the return of the blood flow to normal levels that has stopped or slowed down during ischemia. Ischemia/reperfusion (I/R) is a complex pathological process that starts with insufficient oxygen levels and progresses with a secondary inflammatory response involving neutrophils and reactive oxygen species (ROS) [1, 2]. If the oxygen blood flow, which is used for the continuation of cell functions under normal conditions, is stopped, it causes a series of chemical events that can cause cellular dysfunction. As normal enzyme kinetics change in the cell, high-energy phosphate bonds break down and the cell loses the energy necessary for normal vital balance [1, 3]. In the organisms, there are biological antioxidant enzymes that slow down or stop this negative process under reasonable conditions. However, in some cases, when this process is prolonged, that is, when there is a decrease in the amount of oxygen going to the tissue, the antioxidants in the body are not enough to manage the situation. In cases such as diseases, surgical operations or a decrease in body resistance, taking additional antioxidant materials provides support to the body [4].

Many studies have revealed the role of polyphenols and flavonoids in biological activities such as antioxidant, antimicrobial, and antitumor actions. Silymarin, naringin, and ellagic acid are among the biofunctional components of polyphenols and flavonoids. Phenolic compounds constitute the most important group of water-soluble antioxidants [1, 4].

Silymarin, naringin, and ellagic acid are herbal flavonoid contents isolated from various parts of the plant, and have beneficial effects on varicose veins, menstrual problems, liver diseases, cirrhosis, chronic hepatitis, gall bladder, and cancer. It is stated that they show this effect due to their antioxidant and radical scavenging activity [3-5]. Ether ester bonds of phenolic compounds, such as carboxylic acids, are also common [5, 6].

This study aims to reveal the possible protective effects of silymarin, naringin and ellagic acid, which are known to have antioxidant properties against tissue damage caused by experimentally created short-term ischemia/reperfusion (I/R), by comparing them with blood oxidant and antioxidant enzyme levels.

Material and Methods

The study was conducted in accordance with the Helsinki Declaration. A total of 35 Wistar albino rats, each weighing 250-300 g, were randomly selected and divided into five groups. The rats were housed

in stainless steel wire mesh cages with a temperature control of 24 ± 2 °C, 55% relative humidity and a 12-hour light-dark cycle with 7 rats in each group.

***Table 1**. Diet composition*

Ingredients	**%**
Wheat	10
Corn	23
Barley	15
Wheat bran	8
Soybean	26
Fish flour	8
Meat-bone flour	4
Pelted	5
Salt	0.8
Vitamin mineral mix*	0.2

*Vit A,D_3,E, K_3, B_1, B_2, B_6 and B_{12}, nicotinamid, folic acid, biotin, Mn, Fe, Zn, Cu, I, Co, Se.

To create the remote ischemia-reperfusion model, unilateral lower extremity ischemia was created by compressing the femoral artery with the help of a tourniquet applied to the upper one-third of the thigh after anesthesia.

Group I (Sham group): Sham group (unilateral lower extremity ischemia, followed by a 20-minute ischemia period followed by laparotomy).

Group II (Ischemia-reperfusion group): Control group (the group in which reperfusion was created by unilateral lower extremity ischemia, performing colon anastomosis following laparotomy, and opening the tourniquet after the 30-minute ischemia period was completed).

Group III (Ischemia-reperfusion+Ellagic acid group): to this group; unlike the Ischemia-reperfusion group, 85 mg/kg/day Ellagic acid was orogastrically administered for 10 days after the surgery.

Group IV (Ischemia-reperfusion+Silymarin group): unlike the ischemia-reperfusion group, 200 mg/kg/day Silymarin was orogastrically administered for 10 days after the surgery.

Group V (Ischemia-reperfusion+Naringin group): unlike the ischemia-reperfusion group, 200 mg/kg/day Naringin was orogastrically administered for 10 days after the surgery.

Biochemical Analysis

All the subjects were taken to re-laparotomy on the 10th day of the operation, and the small intestine segment covering the anastomosis area was resected, and their blood samples were obtained for biochemical examinations while the rats were under anaesthesia. The collected blood was centrifuged at 3000 rpm for 10 minutes to obtain plasma and stored at -20 °C until analysis began. Plasma Paraoxonase (PON) activities were analyzed according to Eckerson's [7] method. Plasma TAC and TOC analyzes were performed according to the methods developed by Erel [8] and Erel [9]. Oxidative Stress Index (OSI) indicating the oxidative load is obtained by dividing TOC values to TAC values. Since

TAC result is in mmol/L, it should be converted to µmol/L before the calculation [10]. Plasma TSA and NO analyzes were colorometrically performed via a spectrophotometer according to the methods reported by Sydow and Miranda et al., respectively [11, 12].

Statistical Analysis

Statistical analyzes were performed using the software SPSS, version 25.0. The conformity of the variables to the normal distribution was examined using the Shapiro-Wilk test. Descriptive statistics of quantitative variables were summarized as mean±standard deviation and Median (minimum-maximum) values. A parametric Student's t-Test was used to compare two groups in terms of a normally distributed variable. Non-parametric Mann-Whitney U Test was used for the comparison of two groups in terms of non-normally distributed variables. A parametric Dependent Sample t-Test was used for the comparison of two groups in terms of the quantitative dependent variable with normal distribution. Non-parametric Wilcoxon Ordinal Numbers Test was used to compare two groups in terms of quantitative dependent variables that did not show normal distribution. Cases where $P< 0.05$ were considered statistically significant.

Results

The statistical analysis of blood samples revealed differences in PON (U/L), TAC (mmolTrolx Eq/L), TOC (µmol H2O2 eq/L), TSA (mg/dl), NO (µmol/L), and OSI (Arbitrary unit) between the control, naringin, silymarin, and ellagic acid groups. These differences were analysed using IBM SPSS 25. Descriptor of PON (U/L), TAC (nmolTrolx Eq/L), TOC (µmol H_2O_2 eq/L) TSA (mg/dl) NO ((µmol/L) and OSI (Arbitrary unit) values for blood samples, difference between control, ellagic acid, naringin and silymarin groups and for PON (U/L), TAC (mmolTrolx Eq/L), TOC (µmol H_2O_2 eq/L), TSA (mg/dl), NO (µmol/L) and OSI (Arbitrary unit) values for blood sample statistics are shown in Table 2.

Table 2. *TAC, TOC, OSİ, NO, TSA, PON activitiy in control and Sham, ellagic acid, silymarin, and naringin- treated rats.*

Parameters	Sham (n=7)	Control (n=7)	Ellagic acid (n=7)	Naringin (n=7)	Silymarin (n=7)
PON (U/L)	136.88±16.8^{a}	102.38±15.78^{d}	122.62±16.63^{c}	127.95±19.44^{b}	120.99±17.07^{c}
TAC (mmol Trolox Eq/L)	1.82±0.11^{a}	1.58±0.09^{c}	1.71±0.10^{b}	1.74±0.12^{b}	1.70±0.11^{b}
TOC (µmol H_2O_2 eq /L)	11.0144±1.2^{c}	13.49±1.01^{a}	12.43±1.25^{b}	11.97±1.36^{b}	12.33±1.36^{b}
TSA (mg/dl)	62.33±7.31^{c}	75.17±6.67^{a}	69.70±7.019^{b}	66.69±6.95$^{b.c}$	69.13±7.19^{b}
NO (µmol/L)	13.65±1.53^{c}	22.79±2.01^{a}	19.26±1.93^{b}	17.79±1.72^{b}	18.75±1.77^{b}
OSI (Arbitrary unit)	0.60±0.10^{b}	0.85±0.11^{a}	0.73±0.11^{b}	0.69±0.13^{b}	0.72±0.12^{b}

As a result of the statistical analysis of blood samples, PON (U/L), TAC (mmolTrolx Eq/L), TOC (µmol H_2O_2 eq/L), TSA (mg/dl), NO (µmol/L) and OSI (Arbitrary unit) variables showed normal distribution

which were concluded to be appropriate (P<0.05). [a, b, c]: The difference between the group means shown with different letters in the same row was significant (Table 2).

Table 3. *ANOVA results for blood samples*

Parameters	Group	Average	Standard deviation	The smallest	The biggest	n	F	*P*
PON (U/L)	Sham	136.89	16.81	114.61	157.68	7	3.813	0.012*
	Control	102.39	15.79	81.15	128.80	7		
	Ellagic acid	122.62	16.64	96.79	146.14	7		
	Naringin	127.95	19.45	97.74	155.41	7		
	Silymarin	120.99	17.08	96.09	143.74	7		
TAC (mmol Trolox Eq/L)	Sham	1.83	0.12	1.69	2.00	7	4.226	0.008*
	Control	1.59	0.09	1.48	1.76	7		
	Ellagic acid	1.71	0.10	1.52	1.83	7		
	Naringin	1.74	0.13	1.52	1.91	7		
	Silymarin	1.71	0.11	1.51	1.81	7		
TOC (µmol H_2O_2 eq /L)	Sham	11.01	1.24	9.53	12.94	7	3.561	0.017*
	Control	13.49	1.01	11.80	14.84	7		
	Ellagic acid	12.43	1.25	10.75	14.20	7		
	Naringin	11.98	1.37	9.93	13.80	7		
	Silymarin	12,33	1.36	10.75	14.10	7		
TSA (mg/dl)	Sham	62.33	7.32	51.03	72.93	7	3.102	0.029*
	Control	75,17	6.67	65.83	83.73	7		
	Ellagic acid	69.70	7.02	59.88	81.88	7		
	Naringin	66.70	6.96	55.41	75.38	7		
	Silymarin	69.13	7.20	60.88	81.88	7		
NO (µmol/L)	Sham	13.66	1.53	11.82	16.05	7	23.045	0.000*
	Control	22.80	2.02	19.06	25.23	7		
	Ellagic acid	19.27	1,94	16.66	22.01	7		
	Narinjin	17.80	1.73	15.60	20.03	7		
	Silymarin	18.75	1.77	16.73	21.02	7		
OSİ (Arbitrary unit)	Sham	0.61	0.10	0.48	0.77	7	3.881	0.011*
	Control	0.86	0.11	0.67	1.00	7		
	Ellagic acid	0.73	0.12	0.59	0.94	7		
	Naringin	0.69	0.13	0.52	0.91	7		
	Silymarin	0.73	0.13	0.59	0.93	7		

*P<0.05

A comparative analysis revealed significant differences in key biochemical markers among the experimental groups. The PON value was notably higher in the Sham group compared with the control (P = 0.006). Similarly, the TAC value exhibited a significant increase in the Sham group relative to the control (P = 0.003), while the TOC value showed a marked reduction (P = 0.007). The TSA value also differed significantly between the Sham and control groups (P = 0.014). NO levels considerably varied,

with significant differences observed between the Sham and control groups ($P< 0.001$), as well as between the Sham and ellagic acid groups ($P<0.001$). Additionally, NO levels differed among the control, Sham, ellagic, naringin, and silymarin acid groups ($P<0.001$, $P<0.006$, $P<0.001$, $P<0.002$). The OSI variable was significantly different between the Sham and control groups ($P = 0.004$). Furthermore, the relationships among PON, TAC, TOC, NO, and OSI values were examined through correlation analysis (Table 3), providing further insight into their interconnections.

Discussion

The most reactive free radical in biological systems is reactive oxygen species (ROS), which consists of O^{2-}. ROS alter the normal physiological and chemical structure of the erythrocyte membrane by oxidizing the liposomal membrane, disrupting the ion permeability of the membrane, and causing hemolysis of erythrocytes [13, 14]. Reperfusion leads to rapid production of ROS in ischemia and rapid delivery of molecular O^2 to the tissues. There are many studies on the elimination or reduction of the damage caused by I/R formation [15, 16]. However, there are limited studies on bioactive compounds (silymarin, naringin and ellagic acid) that can prevent the damage caused by I/R in cells and tissues and the changes in blood biochemistry [16, 17].

Plant-based food sources, which are a natural source of antioxidants, contain high levels of phenolic and flavonoid compounds known as ellagic acid, quercetin, naringenin, resveratrol, rutin and hesperidin. It has been reported that these bioactive compounds are a natural source of antioxidants and play an active role in maintaining a healthy life [18-22].

After the end of the reperfusion process following ischemia in rats, the measurement of PON, TAC, TOC, OSI and NO parameters in blood as well as the oxidation and antioxidant levels, and the effect of antioxidant biomaterials used are shown in Table 1. There was a significant difference between the ellagic acid, naringin and silymarin groups ($P<0.05$). After reperfusion, statistically significant increases were detected in blood PON, TAC; TOC, TSA, NO and OSI activities in the I/R+Naringin, I/R+Silymarin and I/R+Ellagic acid groups compared with the I/R. The reason of this increase in antioxidant enzymes after reperfusion was that the over-produced ROS in the I/R event stimulate the antioxidant defence system and the biomaterials used with antioxidant properties strengthen the antioxidant defence system possibly by causing an increase in the expression of CAT, SOD and GSH-Px, which are known as antioxidant enzymes. Thus, they provided a compensatory mechanism created by the body to detoxify the high amount of free radicals formed in the tissues after reperfusion and more antioxidant enzyme production with the drugs given. The fact was that naringin acted as a metal-chelating antioxidant and a free radical scavenger [18, 20]. Clinical studies have shown that complete blood flow to the ischemic organ has not been fully elucidated. It can be said that thrombocyte, interstitial fluid accumulation and reduction of nitric oxide and prostacyclins in the vessel lumen may cause decreased blood flow [23, 24]. Free radicals have been implicated in the pathogenesis of various diseases, including CCl4- and ethyl alcohol-induced liver degeneration and cancer, fluorosis due to

fluoride-induced tissue damage, cadmium-induced nephrotoxicity, and cholesterol-associated fatty liver disease resulting from drug and toxin exposure [14, 25, 26]. It was determined in this study that TAC, PON1 and TSA enzyme activities increased significantly in the Sham group compared with the other group. In another study, in which 6 hours of ischemia and 4 hours of reperfusion were applied, the SOD activity in the lower extremity tourniquet model decreased in the I/R group compared with the control (Sham) group [27]. In another lower extremity tourniquet ischemia model, in which 4 hours of ischemia and 2 hours of reperfusion were applied, the SOD enzyme activity significantly reduced compared with the control group [28]. In the renal I/R study performed by Singh in which 45 minutes of ischemia and 24 hours of reperfusion were applied, with the administration of 400 mg/kg of naringin, the SOD levels in the I/R group decreased compared with the control group, while SOD levels increased in the naringin-treated group, the level of MDA, a lipid peroxidation product, was elevated in the I/R group. It was reported that although it was initially quite high, it decreased and approached the control level in the group treated with naringin [29]. These findings were consistent with the literature. It has been reported that naringin plays an important role in regulating mRNA expressions and increasing SOD and CAT activities in rabbits fed with high cholesterol [30]. These biochemical results support each other. The decrease in antioxidant enzyme activity after reperfusion may be attributed to the increased use of these enzymes due to increased oxidative stress.

These findings show that the protection of tissue damage caused by I/R, which could form free radicals, is probably due to the antioxidant capacity and free radical scavenging activities of naringin and silymarin. It has been shown that ellagic acid which is abundant in raspberry, blackberry, blueberry, strawberry, pomegranate and walnut, induces apoptosis in pancreatic cancer cells and leukemia cells, possesses antioxidant and anti-inflammatory effects and inhibits *in vivo* an *in vitro* tumor growth [6, 22, 28].

Conclusions

In this study, it was concluded that naringin, silymarin and ellagic acid have a protective effect on cells and tissues against I/R damage and can maintain normal blood biochemical values after I/R damage. However, more studies are needed for the use of these natural biomaterials in clinical applications.

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Conflict of Interests The authors stated that there are no conflict of interest in this article.

Authors Contribution Authors contributed equally to the study. All authors read and approved the final manuscript.

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