Eur Arch Otorhinolaryngol (2016) 273:3765–3773
DOI 10.1007/s00405-016-4076-4

RHINOLOGY

Antioxidant activities of curcumin in allergic rhinitis

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Received: 11 February 2016 / Accepted: 29 April 2016 / Published online: 4 May 2016

Abstract We investigated the antioxidant effects of curcumin in an experimental rat model of allergic rhinitis (AR). Female Wistar albino rats ($n = 34$) were divided randomly into four groups: healthy rats (control group, $n = 8$), AR with no treatment (AR + NoTr group, $n = 10$), AR with azelastine HCl treatment (AR + Aze group, $n = 8$), and AR with curcumin treatment (AR + Curc group, $n = 8$). On day 28, total blood IgE levels were measured. For measurement of antioxidant activity, the glutathione (GSH) level and catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) activities were measured in both inferior turbinate tissue and serum. Malondialdehyde (MDA) levels were measured only in inferior turbinate tissue, and paraoxonase (PON) and arylesterase (ARE) activities were measured only in serum. Statistically significant differences were found for all antioxidant measurements (GSH levels and CAT, SOD, GSH-Px activities in the serum and tissue, MDA levels in the tissue, and PON and ARE activities in the serum) between the four groups. In the curcumin group, serum SOD, ARE, and PON and tissue GSH values were higher than the control group. Moreover, tissue GSH levels and serum GSH-Px activities in the curcumin group were higher than in the AR + NoTr group. In the azelastine group, except MDA, antioxidant measurement values were lower than in the other groups. Curcumin may help to increase antioxidant enzymes and decrease oxidative stress in allergic rhinitis. We recommend curcumin to decrease oxidative stress in allergic rhinitis.

Keywords Curcumin · Antioxidant · Allergic rhinitis · Rats

Introduction

Curcumin (diferuloylmethane) is a natural yellow polyphenolic pigment isolated from the rhizomes of the plant *Curcuma longa* L. (turmeric). Curcumin can inhibit the antigen-mediated activation of mast cells, IgE production, airway inflammation, and passive cutaneous anaphylaxis in allergy animal models [1]. It is commonly used as a food additive and it shows a wide spectrum of biological and pharmacological effects, such as anti-inflammatory, antioxidant, antimicrobial, antihepatoxic, hypolipidemic, and anticancer properties [2]. Curcumin also has immunomodulatory and anti-allergic activities [1].

Oxidation is a chemical reaction that transfers electrons from one substance to another; the oxidizing agent becomes chemically reduced by taking away the electrons from its reaction partner, which itself is oxidized. Although such reduction/oxidation (redox) reactions are crucial for life, they can also be damaging [3]. Reactive oxygen species (ROS) are defined as strongly oxidizing chemicals, such as hydrogen peroxide (H_2O_2), ions like hypochlorite (OCI^-),

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most reactive radicals, such as the hydroxyl radical ($OH^{\cdot}$), and the superoxide anion (O_2^{-}). In vivo, ROS are formed as a by-product of cellular respiration in mitochondria [4].

Oxidative stress is thought to contribute to the development of a wide range of diseases, including cardiovascular and neurodegenerative diseases [5, 6]. Early cell death caused by ROS has also been connected with several pathologies that are associated with a chronically activated immune system, such as human immunodeficiency virus infection and acquired immunodeficiency syndrome, and also malignant tumors and autoimmune pathologies [4, 7].

Many herbal antioxidants have been reported, such as ascorbic acid, vitamin E, hesperidin, diosmin, mangiferin, mangostin, cyanidin, astaxanthin, lutein, lycopene, resveratrol, tetrahydro-curcumin, rosmaric acid, hypericin, ellagic acid, chlorogenic acid, oleuropein, andrographolide, potentilla erecta extract, grape seed extract, pycnogenol, green tea extract, white tea extract, and black tea extract [8]. In curcumin, hydroxyl groups largely contribute to its antioxidant and anti-allergic activities [9].

In this study, we investigated the antioxidant activity of curcumin in an allergic rhinitis (AR) induced rat model. The activities of the antioxidant enzymes glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), paraoxonase (PON), and arylesterase (ARE) and malondialdehyde (MDA) levels were assessed to evaluate antioxidant activity.

Materials and methods

This study was conducted in the Faculty of Medicine, Eskisehir Osmangazi University. Animal adaptation, care, and experimental manipulation were performed at TICAM (the Experimental Studies Center of Eskisehir Osmangazi University). Animals were treated in compliance with relevant principles of the Declaration of Helsinki; and Ethics Committee Approval was also taken from Eskisehir Osmangazi University.

Animals

Healthy albino female Wistar rats ($n = 34$, weighing 190–220 g) were used in this study. The experimental protocol was reviewed and approved by the Committee of Ethics of Osmangazi University, Center of Medical and Surgical Experiments. All animal procedures were performed in accordance with the approved protocol.

All rats were housed under the same conditions in a room where the temperature and humidity were controlled (20 ± 1 °C, 50 ± 10 % relative humidity) under a 14/10-h to 16/8-h light/dark cycle. Tap water and standard pelleted food were provided ad libitum.

Experimental design

The 34 rats were divided randomly into four groups:

1. Group 1: Healthy rats (control group, $n = 8$).
2. Group 2: AR with no treatment (AR + NoTr group, $n = 10$): AR was induced, but no treatment was given.
3. Group 3: AR with azelastine HCl treatment (AR + Aze group, $n = 8$): AR was induced and azelastine HCl was given on days 21–28.
4. Group 4: AR with curcumin treatment (AR + Curc group, $n = 8$): AR was induced and curcumin was given on days 21–28.

Methods

Induction of AR

The sensitizing solution was prepared by dissolving 0.3 mg ovalbumin (OVA) (Sigma, St. Louis, MO, USA) in 1 mL saline with 30 mg aluminum hydroxide (40 mg/mL) as an adjuvant. Rats in the AR + NoTr, AR + Aze and AR + Curc groups were injected intraperitoneally with this agent every other day for 14 days (on days 1, 3, 5, 7, 9, 11, and 13; total of seven injections per rat). The rats in the control group were given 1 mL saline plus 30 mg aluminum hydroxide intraperitoneally (total of seven injections per rat) on the same days. After 14 days of systemic sensitization, rats in the AR + NoTr, AR + Aze and AR + Curc groups were given 50 µL 2 % (w/v) OVA-saline solution in the form of intranasal drops into each nostril once daily for 14 days. Rats in the control group received saline drops [6–8]. Each nostril received 25 µL 2 % (w/v) OVA-saline solution or saline [10–13].

Measurement of total IgE levels

On day 28, total serum IgE levels were measured in all groups. Blood samples (1 mL) were centrifuged (3000 rpm, 20 min) and the supernatants stored at −20 °C prior to analysis. Serum IgE levels were determined using a commercially available rat IgE ELISA kit (SunReed Biotechnology Co. Ltd., China) according to the manufacturer's instructions. All results are expressed as kU/L.

Treatment of AR + Aze group

Group 3 rats received azelastine HCl drops in each nostril once daily for 7 days on days 21–28. Drops were given 1 h before intranasal OVA.

Treatment of AR + Curc group

Group 4 rats received curcumin dissolved in distilled water (at 200 mg/mL, 20 μL/nostril) twice daily for 7 days on days 21–28. Drops were given 1 h before intranasal OVA. During curcumin treatment, we did not observe any complications.

Measurement of antioxidant activity

Glutathione (GSH) levels and catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) activities were measured in both inferior turbinate tissue and serum. Malondialdehyde (MDA) levels were measured only in inferior turbinate tissue, and paraoxonase (PON) and arylesterase (ARE) activities were measured only in serum.

Measurement of MDA levels

Tissue MDA levels were determined by thiobarbituric acid (TBA) reaction according to Yagi's method [14]. MDA levels for inferior turbinate tissue are expressed as nmol/mL.

Measurement of CAT activity

Serum and tissue CAT activities were determined according to the method of Aebi et al. [15]. Catalase activity is expressed as U/mg protein for tissue and U/mL for serum.

Measurement of SOD activity

Serum and tissue SOD activities were measured on the basis of the inhibition of nitroblue tetrazolium (NBT) reduction by O_2 generated by the xanthine/xanthine oxidase system. One unit of SOD activity was defined as the amount of protein causing 50 % inhibition of the NBT reduction rate [16]. SOD activity is expressed as U/mg protein for tissue and U/mL for serum.

Measurement of PON and ARE activities

Serum PON and ARE activities were measured spectrophotometrically as described by Eckerson et al. [17] using a molar extinction coefficient of 18,290 mol/L/cm at 412 nm for p-nitrophenol and 1310 mol/L/cm at 270 nm for phenol, respectively. Their activities were determined through calculation of the rates of hydrolysis of paraoxon and phenyl acetate at 25 °C, respectively. PON and ARE activities are expressed as U/mg protein for tissue and U/mL for serum.

Measurement of GSH levels

GSH in tissue or serum was determined by the method of Ellman [18] modified by Jollow et al. [19]. The method is based on the development of a yellow color when DTNB (5,5′-dithiobis-2-nitrobenzoic acid) was added to compounds containing sulfhydryl groups. Serum or homogenized tissue in phosphate buffer (500 μL) was added to 3 mL of 4 % sulfosalicylic acid. The mixture was centrifuged ($3500\times g$, 10 min). Next, 500 μL of the supernatant were taken and added to Ellman's reagent. The absorbance was measured at 412 nm after 10 min. Total GSH content is expressed as μg/mg protein for tissue and μg/mL for serum.

Measurement of GSH-Px activity

The activity of GSH-Px in tissue or serum was determined by the Jocelyn (1970) method [20]. GSH-Px activity is expressed as U/mg protein for tissue and U/mL for serum.

Total protein content

The protein content of inferior turbinate tissues was measured according to the method of Lowry et al. [21] using bovine serum albumin as a standard.

Statistical analysis

The SPSS software (ver. 16.0) was used for statistical calculations. Kruskal–Wallis variance analysis was used to explore differences among the three groups. If a statistically significant difference was apparent, the Mann–Whitney *U* test with the Bonferroni correction was used to identify the parameter causing the difference. A p value of <0.05 was considered to indicate statistical significance. If a Bonferroni adjustment was performed, an adjusted p value of <0.0125 was considered to indicate statistical significance.

Results

The total IgE blood levels were 1656.4, 2766.2, 1223.8, and 1804.5 kU/L in Groups 1–4, respectively. The among-group differences were statistically significant by Kruskal–Wallis variance analysis ($p < 0.05$). The total IgE level of Group 2 was significantly higher than those of Groups 1, 3, and 4 ($p_{\text{adjusted}} < 0.0125$).

Antioxidant measurement results in the four groups are shown in Table 1. For all antioxidant measures (GSH level and CAT, SOD, GSH-Px activities in serum and tissue,

Table 1 Antioxidant measurement results in the serum and tissue for groups 1-4 (Control, AR without treatment, AR with Azelastine HCl and AR with curcumin)

Antioxidant	Group 1 (control) ($n = 8$)				Group 2 (allergic rhinitis without treatment) ($n = 10$)				Group 3 (allergic rhinitis with Azelastine HCl) ($n = 8$)				Group 4 (allergic rhinitis with curcumin) ($n = 8$)				p**
	Median	Min	Max	Mean rank	Median	Min	Max	Mean rank	Median	Min	Max	Mean rank	Median	Min	Max	Mean rank	
Serum SOD (U/mL)	10.15	8.16	11.13	11.50	11.17	9.13	12.76	19.70	10.29	9.05	11.52	12.00	12.13	10.09	14.06	26.25	0.007
Serum Catalase (U/mL)	69.35	61.24	76.51	19.62	72.44	64.57	76.20	23.90	61.42	51.11	66.34	6.50	67.47	62.50	75.19	18.38	0.003
Serum GSH (nmol/mL)	1.56	1.40	1.64	22.25	1.52	1.42	1.73	21.70	1.09	0.83	1.19	4.50	1.50	1.36	1.66	20.50	0.000
Serum GSH-Px (U/mL)	62.11	58.09	63.80	22.38	59.49	56.40	62.48	13.50	58.56	52.05	61.97	9.75	62.25	60.07	65.61	25.38	0.004
Serum PON (U/mL)	96.09	84.33	104.55	11.25	122.40	104.50	137.21	23.80	88.97	82.09	95.11	5.88	127.43	118.82	142.97	27.50	0.000
Serum ARE (U/mL)	1.46	1.24	1.70	13.25	2.21	1.37	2.65	24.30	1.19	1.00	1.37	4.88	2.25	1.60	2.84	25.88	0.000
Tissue SOD (U/mg protein)	6.63	6.01	7.53	16.88	7.08	6.80	7.31	21.90	4.67	4.06	5.34	4.50	7.47	6.38	8.03	25.62	0.000
Tissue Catalase (U/mg protein)	14.44	13.50	15.39	25.88	12.86	11.09	14.63	16.55	10.24	8.24	11.34	4.62	13.94	12.34	16.34	23.19	0.000
Tissue GSH (nmol/mg protein)	245.03	220.94	258.09	16.50	252.38	234.39	264.32	19.70	145.87	133.90	162.42	4.50	274.50	236.70	294.37	28.75	0.000
Tissue GSH-Px (U/mg protein)	0.79	0.69	0.85	18.44	0.83	0.64	0.89	22.35	0.54	0.41	0.67	4.75	0.83	0.67	0.94	23.25	0.000
Tissue MDA(nmol/mg protein)	25.01	14.67	29.80	20.88	20.69	10.27	24.34	12.50	30.96	22.41	36.94	28.62	16.98	9.40	22.93	9.25	0.000

AR allergic rhinitis

** p values derived via Kruskal–Wallis variance analysis. A p value of <0.05 was considered to indicate statistical significance

MDA level in tissue, and PON and ARE activities in serum), the differences between the four groups (Control, AR + NoTr, and AR + Curc groups) were found as statistically significant ($p < 0.05$).

SOD (serum and tissue)

In the curcumin group, serum SOD activity was significantly higher than in the control group. In the azelastine group, the tissue SOD level was significantly lower than in the three other groups (adjusted $p < 0.0125$; Table 2).

CAT (serum and tissue)

Serum and tissue CAT activities in the azelastine group were significantly lower than those in the three other groups (adjusted $p < 0.0125$; Table 2).

GSH (serum and tissue)

Serum and tissue GSH levels in the azelastine group were significantly lower than those in the three other groups. Additionally, tissue GSH level in the curcumin group was significantly higher than in the control group and AR + NoTr group (adjusted $p < 0.0125$).

GSH-Px (serum and tissue)

Serum *GSH-Px* activity in the control and curcumin groups was significantly higher than in the azelastine group. In the curcumin group, serum *GSH-Px* activity was significantly higher than in the AR + NoTr group (adjusted $p < 0.0125$). Tissue *GSH-Px* activity in the azelastine group was significantly lower than in the three other groups (adjusted $p < 0.0125$; Table 2).

Serum ARE

Serum ARE activity in the curcumin and AR + NoTr groups was significantly higher than in the control group. Serum ARE activity in the azelastine group was significantly lower than in the three other groups (adjusted $p < 0.0125$; Table 2).

Serum PON

Serum PON activity in the curcumin and AR + NoTr groups was significantly higher than in the control group and azelastine groups (adjusted $p < 0.0125$; Table 2).

Tissue MDA

Tissue MDA levels in the curcumin and AR + NoTr groups were significantly lower than those in the azelastine group (adjusted $p < 0.0125$; Table 2).

Discussion

Curcumin (diferuloylmethane) [22], present in the rhizome of the plant *Curcuma longa*, possesses strong antihepatotoxic [23], antioxidant [24], anti-inflammatory [25] and antitumour [26] activities. It also prevents the initiation of proliferation, invasion, angiogenesis, and metastasis in different cancer cells by interacting with the different cell signaling proteins in mice and rats [27].

Antioxidant compounds are capable of neutralizing ROS, which represents an important aspect of the proinflammatory cascade and Th1-type immunity [28]. To counteract the harmful effects of ROS, cells have a variety of defense strategies, among which are several small molecules that function as antioxidants, as well as two major enzymes, catalase and superoxide dismutase, which are induced to neutralize ROS biochemically [29–31].

Antioxidants also terminate oxidative chain reactions by removing free radical intermediates [31]. Antioxidants may be synthesized in the body or obtained from the diet, as many normal food compounds are antioxidants. They are especially abundant in fruits and vegetables, such as bananas, cranberries, apples, dates, red grapes, potatoes, tomatoes, as well as in beverages, such as coffee, cocoa, and tea. In recent years, glutathione, ascorbic acid (vitamin C), carotenes (vitamin A), melatonin, tocopherols, and tocotrienols (vitamin E) have been under intense investigation with regard to their capacities as antioxidants and in free radical neutralization [32].

Antioxidants may promote health and reduce the effects of aging by cancelling out the cell-damaging effects of free radicals [4]. Various antioxidant compounds have been demonstrated to suppress features of the Th1-type immune response. These agents include not only vitamins, antioxidant phytochemicals, plant extracts, and beverages, but also food preservatives, like sodium sulfite, benzoate, and sorbate, and colorants, like curcumin and beet root extract [33]. Suzuki et al. [34] reported that the hydroxy groups of curcumin play a significant role in exerting both the anti-oxidative and anti-allergic activities, and that most of the compounds develop the anti-allergic activities through mechanisms related to anti-oxidative activities, but some through mechanisms unrelated to anti-oxidation activity.

In this study, we investigated the effects of curcumin in an experimental rat model of AR. Antioxidant

Table 2 Pair-wise comparisons between groups 1–4 (Control, AR without treatment, AR with Azelastine HCl and AR with curcumin) using the Mann–Whitney *U* test with Bonferroni adjustment for antioxidant measurement results in the serum and tissue

Antioxidant	Pairwise comparison											
	Group 1–2		Group 1–3		Group 1–4		Group 2–3		Group 2–4		Group 3–4	
	z	$p_{adjusted}$ ▲	*z*	$p_{adjusted}$ ▲	*z*	$p_{adjusted}$ ▲	*z*	$p_{adjusted}$ ▲	*z*	$p_{adjusted}$ ▲	*z*	$p_{adjusted}$ ▲
Serum SOD (U/mL)	−1.866	0.062	−0.210	0.834	−2.626	0.009	−1.866	0.062	−1.777	0.076	−2.626	0.009
Serum Catalase (U/mL)	−0.977	0.328	−2.626	0.009	−0.315	0.753	−3.288	0.001	−1.422	0.155	−2.731	0.006
Serum GSH (nmol/mL)	−0.089	0.929	−3.361	0.001	−0.525	0.600	−3.554	0.000	−0.267	0.790	−3.361	0.001
Serum GSH-Px (U/mL)	−1.955	0.051	−2.521	0.012	−0.735	0.462	−0.977	0.328	−2.577	0.010	−2.836	0.005
Serum PON (U/mL)	−3.465	0.001	−2.205	0.027	−−3.361	0.001	−3.554	0.000	−1.422	0.155	−3.361	0.001
Serum ARE (U/mL)	−2.932	0.003	−3.046	0.002	−3.151	0.002	−3.554	0.000	−0.444	0.657	−3.361	0.001
Tissue SOD (U/mg protein)	−1.601	0.109	−3.363	0.001	−1.997	0.046	−3.556	0.000	−1.245	0.213	−3.361	0.001
Tissue Catalase (U/mg protein)	−2.488	0.013	−3.361	0.001	−.735	0.462	−3.465	0.001	−1.822	0.068	−3.361	0.001
Tissue GSH (nmol/mg protein)	−1.155	0.248	−3.361	0.001	−2.836	0.005	−3.554	0.000	−2.754	0.006	−3.361	0.001
Tissue GSH-Px (U/mg protein)	−1.200	0.230	−3.361	0.001	−1.155	0.248	−3.465	0.001	−0.355	0.722	−3.256	0.001
Tissue MDA(nmol/mg protein)	−2.044	0.041	−1.995	0.046	−2.415	0.016	−3.465	0.001	−1.066	0.286	−3.256	0.001

AR allergic rhinitis

▲ $p_{adjusted}$: Mann–Whitney *U* test/Bonferroni adjustment data. $p_{adjusted} < 0.0125$ was considered to indicate statistical significance

measurements were performed in all four groups. Statistically significant differences were found for all antioxidant measurements (GSH level and CAT, SOD, GSH-Px activities in serum and tissue, MDA levels in tissue, and PON and ARE activities in serum) between the four groups. In the curcumin group, serum SOD, ARE, and PON, and tissue GSH values were higher than in the control group. Moreover, tissue GSH level and serum GSH-Px activity in the curcumin group were higher than in the AR + NoTr group. In the azelastine group, except for MDA, antioxidant measurement values were lower than in the other groups.

In a guinea pig model with induced allergic rhinitis, curcumin reduced allergy-related symptoms, such as sneezing, rubbing frequency, lacrimation, and nasal congestion, and reduced inflammatory cell infiltration of the nasal mucosa [35]. Curcumin also inhibited house dust mite-induced lymphocyte proliferation and IL-2, IL-5, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-4 production in vivo [36]. The antioxidant mechanisms of garlic and curcumin have been attributed to their ability to scavenge ROS through modulation of cellular antioxidant enzyme activity and GSH levels [37–41]. Curcumin has an anti-allergic effect through modulating mast cell-mediated allergic responses in AR. It also inhibited the histopathological changes of nasal mucosa, and decreased the serum levels of histamine, OVA-specific IgE and TNF-α in OVA-induced allergic rhinitis mice. In addition, curcumin suppressed the production of inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8 [42]. Curcumin also inhibits the arachidonate 5-lipoxygenase (5-LOX) enzyme [43] and cyclooxygenase (COX) enzyme. Two main enzymes of COX and LOX are responsible for the production of eicosanoids. Inhibition of these two enzymes delays tumorigenesis in animals and humans [44].

Curcumin has antioxidant and anti-inflammatory properties [45]. Curcumin inhibits lipid peroxidation and oxidative DNA damage, and reduces the release of arachidonic acid through lipoxygenase and cyclooxygenase inhibition. Curcumin facilitates excretion of many oxygen radicals, particularly superoxide anion, nitrogen dioxide, and hydrogen radicals. Moreover, curcumin shows an anti-inflammatory effect by inhibiting NFκB activation [46, 47]. Curcumin decreased TNF-α and IL-1β levels by preventing inflammation [48]. Curcumin play a vital role against free radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins as an antioxidant activity. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit COX-2, LOX, and inducible nitric oxide synthase (iNOS) whose are important enzymes that mediate inflammatory processes. Upregulation of COX-2 and/or iNOS has been associated with inflammatory disorders [45].

Yarru et al. [49] observed that dietary curcumin increased the expression of hepatic GSH-Px when compared with controls and the expression of the GSH-Px gene was not significantly decreased in birds fed AFB1, where the indirect antioxidant capacity of curcumin was defined by its ability to induce the expression of GSH-Px. Curcumin has relatively low toxicity in human subjects [50]. Large doses of curcumin can cause gastrointestinal problems, including diarrhea and constipation, and in rare cases, contact dermatitis [51, 52]. Curcumin has potential for topical therapy in various allergic diseases, including allergic rhinitis, especially in view of its low toxicity in human subjects [53].

Curcumin, with its antioxidant properties, reduces the oxidative stress that occurs in allergic rhinitis. Because curcumin is an herbal product, and the adverse reactions were limited, it may be suggested for use in people with allergic rhinitis. As an example, curcumin products may be added to yogurt, so it may be used as a nutritional supplement in people with allergic rhinitis. For this purpose, bioavailability should be investigated in detail. These products can be considered as products that will enhance the quality of life. We recommend further research to investigate this issue.

We conclude that curcumin may help to increase antioxidant enzymes and lead to a decrease in oxidative stress in allergic rhinitis. We recommend curcumin for decreasing oxidative stress in allergic rhinitis.

Acknowledgments With the exception of data collection, preparation of this paper, including design and planning, was supported by the Continuing Education and Scientific Research Association.

Compliance with ethical standards

Conflict of interest Author Niyazi Altıntoprak declares that he has no conflict of interest. Author Murat Kar declares that he has no conflict of interest. Author Mustafa Acar declares that he has no conflict of interest. Author Mehmet Berkoz declares that he has no conflict of interest. Author Nuray Bayar Muluk declares that she has no conflict of interest. Author Cemal Cingi declares that he has no conflict of interest.

Ethical approval Animals were treated in compliance with relevant principles of the Declaration of Helsinki; and Ethics Committee Approval was also taken from Eskisehir Osmangazi University. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Article does not contain studies with human participants.

Informed consent Informed consent is not needed, because Article does not contain studies with human participants.

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