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Effects of Resveratrol on Oxidative DNA Damage Induced by the Acute Swimming Exercise

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Authors' contributions

This work was carried out in collaboration between all authors. Author FKC designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MA and RL managed the analyses of the study. Author IC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: The point of this study was to look at how resveratrol administration affects on intense swimming exercise in oxidative circumstance. The investigation may suggest the administration of resveratrol supplements for athletes who are practice intensely.
Methods: In this research, rats were isolated into four groups, and there were eight rats in each group.
Group 1 was the control group which was not subjected to any application. Group 2 was the control group subjected to exhaustive exercise. Group 3 was Resveratrol-supplemented swimming group. This group was administered with 10 mg/kg/day Resveratrol intraperitoneally for a month and enforced exhaustive exercise at the end of applications. Group 4 was Resveratrol supplemented

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general control group which managed with 10 mg/kg/day Resveratrol intraperitoneally for a month and not subjected to exercise toward the finish of the application. Malondialdehyde (MDA), total oxidant levels (TOS), total antioxidant levels (TAS) and eight hydroxy guanosine (8-OhdG) levels were assessed in this study.

Results: In this examination, highest MDA levels and TOS in intense swimming exercise were found ($p < 0.05$). Additionally, intense swimming exercise was caused by DNA damage in mononuclear leukocytes and raised 8-OhdG levels and TAS ($p<0.05$).

Conclusion: Resveratrol was diminished severity of oxidative DNA damage, genotoxicity and lipid peroxidation of intense swimming exercise. Taking everything into account, resveratrol has ameliorative effects against lipid peroxidation and genotoxicity by expanding antioxidant defence mechanism in rats.

Keywords: Rat; supplements; peroxidation; DNA.

1. INTRODUCTION

Resveratrol (3,5,40-trihydroxystilbene) is a polyphenol found in grapes (*Vitis vinifera*), an assortment of berries, peanuts, and therapeutic plants, such as Japanese knotweed (*Polygonum cuspidatum*) [1]. The most vital dietary wellspring of resveratrol is wine. Resveratrol was first appeared to avert carcinogenesis in mice [2]. In the next years prominent for its anti-inflammatory, anti-tumorigenic, and anti-oxidant properties, and also its capacity to enlarge lifetime in lower organisms and enhance general wellbeing in mammals [3]. The oxidant–antioxidant balance is an imperative mechanism for homeostasis in a life form. Reactive oxygen species [ROS), for example, superoxide radical anions, hydroxyl radicals, and hydrogen peroxide, are composed because of different metabolic and physiological procedures, and destructive oxidative reactions may happen. Oxidative stress is depicted to happen when the harmony amongst oxidant and antioxidant is moved to the toward oxidants side [4]. Exhaustive exercise is known to prompt oxidative damage from produced reactive oxygen radicals in various tissues. [5]. Exhaustive physical exercise is known to cause oxidant damage, likely by advancing free radical production in numerous tissues, including muscle, liver, heart and lungs in animals. There is a growing proof demonstrating that intemperate exercise can enhance oxidative stress and prompt a rise in the antioxidants requirement [6]. Resveratrol has been exhibited to diminish oxidative stress, and these systems may represent most its medical advantages [7]. Our experiment was focused on the antioxidant activity of resveratrol against the free radical generation of exhaustive exercise. Oxidative stress particularly prompts the DNA damage [8]. Oxidative stress happens when an abundance of reactive oxygen species (ROS) are delivered from any of an assortment of sources, including the mitochondrial electron transport chain and decreased nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases [9].

The point of this work was to investigate the impacts of Resveratrol on lipid peroxidation, antioxidant status and DNA damage in rats to intense swimming activity [10].

2. MATERIALS AND METHODS

2.1 Materials

Resveratrol was obtained from Sigma-Aldrich (Interlab, Turkey). All the other chemicals and reagents were of analytical reagent grade obtained from commercial sources. Normal melting point agarose (NMPA), low melting point agarose (LMPA), di-sodium salt of the ethylene diamine tetra acetic acid (EDTA), Tris buffer, ethidium bromide (EtBr), Trizma base, Tris HCl and Triton X-100, SDS were purchased from Sigma-Aldrich (Interlab, Turkey).

2.2 Experimental Protocol

This investigation was directed at Kobay Experimental Animals laboratory in Ankara (Turkey). Thirty-two Spraque-Dawley type grown-up male rats were gotten from the Experimental Animals Unit. Kobay Experimental Animals Ethics Committee has endorsed this investigation with protocol no 2013/75.

Experimental animals utilized as a part of the examination were equally divided into four groups:

Group 1 : General control group was not subjected to any procedure.

Group 2 : The control group was subjected to exhaustive exercise.

Group 3 : Resveratrol-supplemented swimming group. This group was administered with 10 mg/kg/day Resveratrol intraperitoneally for a month and applied with exhaustive exercise at toward the finish of applications [11].

Group 4 : Resveratrol supplemented general control group. This group was administered with 10 mg/kg/day Resveratrol intraperitoneally for a month and not subjected to exercise toward the finish of the application [11].

The test animals were fed with 10 g fodder (standard rat feed) per 100 g of body weight day by day. They were kept in a situation with 12 h dark/12 h light cycles and at standard room temperature (21±1ºC). Toward the finish of one month test period, the rats were executed under anaesthesia during the 9– 10 AM period. Samples of the biochemical examination were put away at −20ºC until the time of investigations.

2.3 Swimming Exercise

The activity was performed in a warmth safe glass swimming pool, which was 50 cm depth and width and had a thermostat to keep the temperature settled at 37ºC. The activities were done once for 30 min, 24 h after the finish of procedures. After the experimental animals were made to swim in sets, they were executed so blood samples might be gathered for investigations [12].

2.4 Biochemical Analyses

2.4.1 MDA and GSH levels

Blood samples were isolated into the serum. Whole blood (MDA) was figured by utilizing the technique for Draper and Hardley [13]. This technique depends on the coupling of MDA with thiobarbituric acid. Whole blood diminished glutathione (GSH) concentrations were tested by utilizing the colourimetric technique for Beutler et al. [14]. A Shimadzu UV-1601 visible spectrophotometer (Kyoto, Japan) was utilized for blood and tissue biochemical investigation.

2.4.2 Measurement of the TAS in serum

Serum TAS level was estimated by utilizing a novel automated colourimetric measurement technique created by Erel [15]. The principle of this estimation technique depends on the oxidation of the 2.20 - and-bis (3-ethylbenzthiazoline-6-sulphonic corrosive) (ABTS) molecule to the ABTS molecule within sight of hydrogen peroxide. The rate of the reaction was aligned with the standard method for Trolox which is a vitamin E analogue, and its unit was mmol Trolox Equivalent/L.

For the measurement of TAS in serum, some procedures were followed. Firstly, 500 microliter Reagent 1 was put into the cell, and 30 microliter standard (or sample) was included. The first absorbance was taken at 660 nm for the first absorbance point. 75 microliter Reagent 2 was added to the cell and incubated for 10 minutes at room temperature or 5 minutes at 37ºC. The second absorbance was taken at 660 nm.

Calculating the Results

Result = ∆ Absorbance Standard1= (Second Absorbance of Std1- First Absorbance of Std1) ∆ Absorbance Standard2 = (Second Absorbance of Std2- First Absorbance of Std2) ∆ Sample Absorbance = (Second Absorbance of Sample-First Absorbance of Sample)

2.4.3 Measurement of the TOS in serum

The total oxidant level was estimated utilizing a completely automated colourimetric technique created by Erel [16]. The rule of this strategy depends on the oxidation of ferrous ion–o-dianisidine complex to ferric ion by the oxidants exhibit in the sample. The density of the colour, which is associated with the measure of oxidants in the sample, was estimated by using spectrophotometry. The examine adjusted with hydrogen peroxide, and the data were expressed as micromolar hydrogen peroxide equivalent per litre (Imol H2O2 Equiv/L).

For the measurement of TOS in serum, some procedures were followed. The working standard solution was prepared. SSSS was weakened 40,000 times with deionised water. For the initial step of dilution, a liquid of 50 microliters SSSS was added to 10 ml deionised water and vortexed. For the second step of dilution, a liquid of 50 microliters of the prepared solution was added to 10 ml deionised water and vortexed.

The last concentration of the working standard was 20 micromolar H2O2. The working solution was prepared every day. 500 microliter Reagent 1 was added to the cell and 75 microliters the prepared standard (or sample) was added. The first absorbance was taken at 530 nm for first absorbance point. 25 microliter Reagent 2 was added to the cell and incubated for 10 minutes at room temperature or 5 minutes at 37ºC. The second absorbance was taken at 530 nm.

Calculating the Results

Result = (AbsSample / AbsStandard2) X 20 (Standard2 Value) Sample Absorbance = (Second Absorbance of Sample - First Absorbance of Sample) Absorbance Standard 2 = (Second Absorbance of Std 2 - First Absorbance of Std 2) Standart 2 Value = 20 µmol H2O2 Equiv./

2.4.4 Measurement of 8-OHdG in serum

The serum samples were analyzed for their concentration of 8-hydroxy-2' - deoxyguanosine (8-OHdG) utilizing a competitive enzyme immunoassay (EIA) kit (Cayman Chemical Company, Ann Arbor, MI, USA) and intra- assay and inter-assay CV were determinate 5.3% and 8.2 %, respectively.
For the measurement of 8-OHdG in serum, some procedures were followed.

1) Wells were specified for diluted standard, blank and sample. 5 wells were set up for standard points; 1 well for blank, 50µL each of dilutions of standard (read Reagent Preparation), blank and samples were set into the proper wells, separately. And after that 50µL of Detection Reagent A was put to each well instantly. The plate was shaken tenderly. The plate was secured with a plate sealer and incubated for 1 hour at 37ºC. Detection Reagent A may seem shady. It was warm to the room temperature and blend delicately until the solution seems uniform.
2) The solution was aspirated and washed with 350 µL of 1X Wash Solution to each well utilizing a squirt bottle, multi-channel pipette, manifold dispenser or autowasher, and let it sit for 1-2 minutes. The staying fluid was expelled from all wells totally by snapping the plate onto permeable paper. The procedure was rehashed three times. After the last wash, any remaining was evacuated with wash buffer by aspirating or tapping. The plate was inverted and bloated against absorbent paper.
3) 100µL of Detection Reagent B working solution was put into each well and incubated for 30 minutes at 37ºC in the wake of covering the plate with the plate sealer.
4) The aspiration/wash process was rehashed for 5 times totally as led in stage 2.
5) 90µL of Substrate Solution was put into each well. The plate was secured with another plate sealer and incubated for 10-20 minutes at 37ºC. It was shielded from light. The liquid was turned blue by the addition of Substrate Solution.
6) 50µL of Stop Solution was put into each well. The liquid was turned yellow by the addition of Stop arrangement. The liquid was blended by tapping the side of the plate. The plate was tap tenderly to guarantee intensive blending if colour change did not seem uniform.
7) Any drop of water and mark on the base of the plate was evacuated, and it was affirmed that there was no bubble on the surface of the liquid. At that point, the microplate reader was run, and determination at 450 nm was led instantly.

2.5 Comet Assay in Rat Mononuclear Leukocytes

Mononuclear leukocytes were isolated to utilize income assay. For this, the technique for Kocyigit et al. [17] was taken after. In this technique; heparinized blood samples were spilled into histopaque 1077 on the test tubes and after shaping a small layer the test tubes were centrifuged at 2100 rpm for 30 min [25ºC]. From that point forward, the center layer (contains mononuclear leukocytes) was moved into 1 mL of salinized phosphate buffer(PBS) (pH 7.4) and blended with it. At that point, this mixture was again centrifuged at 1600 rpm for 10 min (25ºC). After releasing the supernatant, the pellet was diluted as including 10^6 in mm^3 by PBS (pH 7.4). After that, leukocytes were blended with 100 µL of 0.5% low-melting agarose in PBS at 37ºC. In this way, 80 µL of this mixture was layered onto a slide pre-covered with a thin layer of 1% normal melting point agarose, secured quickly with a coverslip and put away for 5 min at 4ºC to permit the agarose to harden. Subsequent to evacuating the cover-slips, the slides were drenched in newly prepared cool (4ºC) lysing solution (2.5 M NaCl, 100 mM EDTA-Na2; 1%

Na-sarcosine, 10 mM Tris– HCl, pH 10– 10.5; 1% Triton X-100 with 10% DMSO being included just before use) for no less than 1 h. The slides were then electrophoresed (25 V/300 mA, 25 min) after they were drenched in newly prepared alkaline electrophoresis buffer (0.3 M NaOH and 1 mM EDTA-Na2, pH > 13) at 4ºC for loosening up (40 min). All steps were completed under a negligible light. After electrophoresis, the slides were neutralized (0.4 M Tris– HCl, pH 7.5) for 5 min. The dried microscope slides were stained with two µg mL−1 ethidium bromide (70 µL/slide), secured with a cover-slip each and investigated by utilizing a fluorescence microscope. The pictures of 100 haphazardly picked nuclei were investigated visually. Perceptions were made at amplification of 400× by utilizing a fluorescent microscope (Olympus, Japan). Each picture was grouped by the power of the fluorescence in the comet tail by being given a value of 0, 1, 2, 3 or 4 (from unharmed class 0 to maximally harmed class 4), and in this way the total score of the slides was ranged from 0 to 400 arbitrary units (AU). Harm was recognized by a tail of divided DNA that relocated from nuclei, causing a 'comet' pattern, though entire nuclei, without a comet, were not viewed as harmed.

2.6 Statistical Analyses

Data got from test animals were stated as means and standard deviation of means (±SD) and analyzed utilizing one-way analysis of variance (ANOVA) [18], trailed by Duncan post-hoc tests on the SPSS (18.0] software computer program. A distinction in the mean values of $p<0.05$ was thought to be significant.

3. RESULTS

3.1 Effect on MDA and GSH Levels

MDA level is generally utilized a marker of free-radical mediated LPO. An exceedingly huge rise was seen in the blood, liver ($p <0.05$) MDA levels of intense swimming exercise performed rats contrasted with a control group (Table 1). GSH is a non-enzymatic antioxidant in the detoxification pathway that diminishes the toxic metabolites of different toxicants. Whole blood and tissue ($p <0.05$) GSH levels in the intense swimming exercise group were discovered essentially lower than a control group. Interestingly, administration of group 4 was demonstrated importantly expanded GSH levels compared to the group 2 and group 3 (Table 1). Results were demonstrated that, MDA levels were importantly diminished in resveratrol treatment groups and GSH levels were fundamentally expanded in resveratrol treatment groups.

3.2 Effect on Total Oxidant – Total Antioxidant Capacity

Serum TAS and TOS of a control group, group 2, group 3 and group 4 were given in (Table 1). The serum TOS were significantly higher and TAS significantly lower in the group 2 in contrast with the control, group 4. ($p <0,05$). Comparison of Swimming Exercise-Swimming Exercise after Resveratrol administration TOS, TAS and OSI were shown a statistically significant wane in TOS ($p<0.05$) and statistically significant increment in TAC ($p<0.05$) after Resveratrol administration. Resveratrol was diminished that TOS levels in exhaustive exercise groups which TOS levels were expanded and TAS levels were expanded.

3.3 Effect of 8-OHdG Markers

The serum 8-OHdG data for the assessment of intense Swimming Exercise was outlined in Table 1. There was a huge increment of serum 8-OhdGlevels in group 2 when contrasted with the control group. Resveratrol was diminished 8-OHdG levels in exhaustive exercise groups.

3.4 Effect on DNA Damage

DNA damage was detected in mononuclear leukocytes of rats and demonstrated at Fig. 1 and Table 2. In the group 2, DNA damage levels were observed to be high level (13.5±4.63 AU) compared to Group 1 (4.16±0.75 AU) ($p < 0.05$). DNA damage was additionally observed to be at 5±1.54 and 8.66±1.03 AU in group 3 and group 4, individually. DNA damage was diminished after group 4 contrasted with group 2 and these values were considered statistically significant. Resveratrol was diminished DNA damage in the exhaustive exercise group.

4. DISCUSSION

Oxidative stress is really defined as the unevenness amongst oxidants and antioxidants in biological systems. Physical stressors, for example, intense aerobic, anaerobic and severe exhaustion exercise can bring about extraordinary reactive oxygen production [18,19,20]. In this regard, the superoxide radical ($O2^{\bullet -}$), is thought to be the pioneer of ROS

Table 1. Effects of Resveratrol on Malondialdehyde (MDA), TAS, TOS levels in blood and liver

Group	MDA blood (nmol/ml)	MDA liver (nmol/g tissue)	TOS blood (μmol H2O2 Equiv./L)	TAS blood (mmol Trolox Equiv./L)
Group 1	4.16±1.52[a]	0.20±0.02[a]	0.46±0.03[a]	0.36±0.06[a]
Group 2	11.52±1.02[b]	2.41±0.36[b]	0.73±0.06[b]	0.16±0.03[b]
Group 3	3.41±1.35[a]	0.25±0.03[a]	0.37±0.05[a]	0.41±0.02[a]
Group 4	8.09±0.80[c]	1.34±0.47[c]	0.43±0.08[a]	0.28±0.06[c]

a,b,c In the same column values with different letters show statistically significant differences in blood and liver MDA, levels and blood TAS, TOSlevels (p<0.05).Mean±SD: Standard Deviation

Table 2. Effects of Resveratrol on Glutathione (GSH), 8-OHdG and DNA levels in blood and liver

Group	GSH blood (mg/dL)	GSHLiver (mg/g tissue)	8-OhdG blood (ng/ml)	DNAdamage (Arbitrary Unit ±SD)*
Group 1	448.06±32.55[a]	6.48±0.32[a]	4,78±0,51[a]	4.16±0.75[a]
Group 2	84.62±2.51[b]	1.04±0.17[b]	8,84±0,36[b]	13.5±4.63[b]
Group 3	456.86±21.9[a]	6.55±0.28[a]	4,88±0,49[a]	5±1.54[a]
Group 4	269.72±25.5[c]	3.59±0.13[c]	6,72±0,39[c]	8.66±1.03[c]

*a,b,c In the same column values with different letters show statistically significant differences in blood and liver GSH levels and blood 8-OHdG and DNA levels (p<0.05). * Means with the same letter do not differ statistically at the level of 0.05 M; Mean±SD: Standard Deviation*

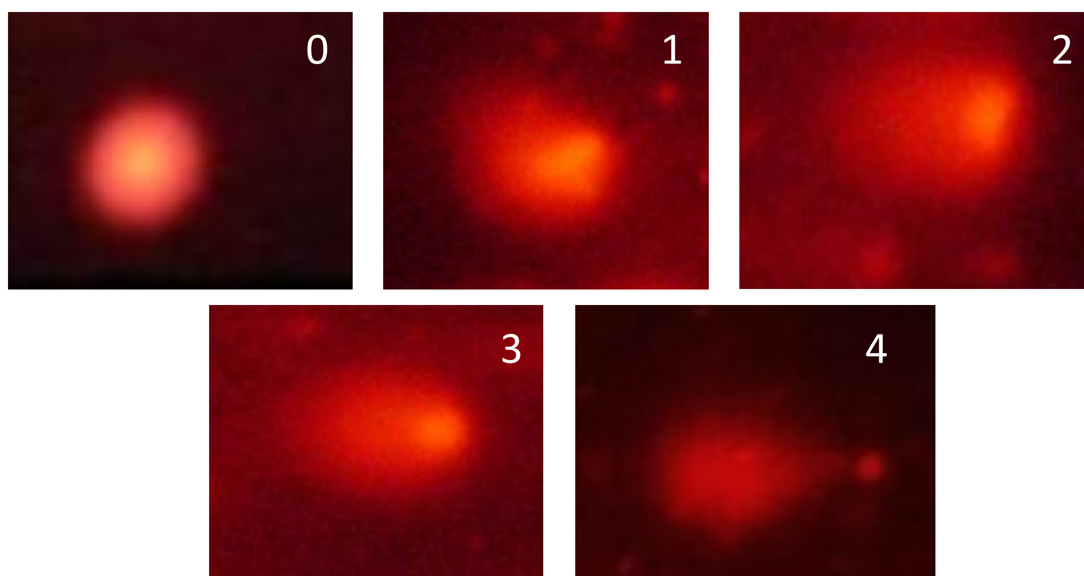

Fig. 1. Visual scoring of DNA damage from 0 to 4 according to comet appearance in rat mononuclear leukocytes

including OH• , RO• , ROO• and H2O2 (16]. For instance, the superoxide radical (O2•-) can respond with nitric oxide (•NO), an exceptionally reactive molecule, the peroxynitrite anion (ONOO-), likewise entitled a reactive oxygen and nitrogen species (RONS), able to cause DNA fracture and lipid oxidation [21,22]. Davison et al. [23] demonstrated that intense exercise expanded DNA damage, notwithstanding the supplementation of antioxidant substances. Regardless of opposing data, it is, for the most part, concurred that physical exercise expands free radical development [24]. Extreme physical activity was appeared to prompt oxidative stress in the blood and different tissues of people, as well as animals [25].

Expanded oxidative stress alludes to an nonequilibrium between the intracellular generation of free radicals and the cell resistance

components, and MDA is a standout amongst the most critical oxidative stress markers [26]. This finding of our own shows that MDA levels are lifted by intense swimming activity. High MDA levels in intense swimming exercise are reliable with the outcomes of Akil et al. [27]. Demonstrated in their study that acute exercise significantly increased MDA levels in acute swimming exercise rats [28]. When antioxidant defences are debilitated, body cells and tissues turn out to be more inclined to create dysfunction as well as an ailment. In this investigation, TAS levels diminished in intense swimming exercise. Oxidative stress might be happening in exhaustion exercise, and like this total antioxidant capacity have diminished. High total antioxidant levels (TOS) upheld that exercises made oxidative stress. High MDA levels acquired from group 3 are steady with the results of the analysts cited above. Ji et al. [29] demonstrated that resveratrol administration significantly diminished MDA concentration in blood and liver and TOS levels in the blood, which demonstrates that there is a difference in the diminished free radical damage in cells between resveratrol supplementation. Free radical development and antioxidant activity enlarge with work out. It is far from being obviously true whether this expansion is connected by the time of exercise [30,31]. It was accounted for that exercise prevented the damage caused by free radicals in rats [29]. It was additionally recorded that aerobic exercise raised free radical development [32] and that antioxidant activity was induced in reply to exercise [33].

There is a huge trial archive that oxidative damage permanently consist of lipids of cellular membranes, proteins, and DNA. In nuclear and mitochondrial DNA, 8-hydroxy-2' - deoxyguanosine [8-OHdG) or 8-oxo-7,8-dihydro-2' - deoxyguanosine (8-oxide) is one of the overriding forms of free radical-induced oxidative lesions, and has thus been commonly used as a biomarker for oxidative stress. Our discoveries demonstrate that elevated levels of 8-OHdG happened in the serum of intense swimming exercise rats. In the present examination, resveratrol administration advanced the GSH level in blood and liver an accompanying decrease in lipid peroxidation. DNA damage actuated by free radicals is significant since its launch and support carcinogenesis [28]; DNA is liable to attack by free radicals roughly 10.000 times each day [34]. Lately, diverse mechanisms have been elevated to clarify the antioxidant activity of the vast majority of the polyphenols, like RSV, which is related with no less than three procedures: 1) expanded level of intracellular GSH, 2) constriction of Ca2 + influx, 3) evacuation of ROS or inactivation of free radicals by the donation of hydrogen particles [35,36]. As to DNA- protection system for RSV initiated by an oxidative compound, for example, DDS-NHOH, different authors additionally announced that $NaAsO_2$ exposure prompted an abatement of cell proliferation and increment in DNA/chromosomal damage and apoptotic cell death, for the most part using oxidative stress. While cells treated with RSV demonstrated enhanced cell survival and decreased DNA/chromosomal damage, oxidative stress and apoptosis [37].

Likewise, Chiavaroli et al. demonstrate that the antioxidant effects of resveratrol in rat brain could assume a neuroprotective part in maturing, when the expanded burden of oxidative stress is looked by defective antioxidant mechanisms [38].

The report by Veera Reddy et al. [39] to the effect that antioxidant enzymes expanded in response to exercise is consistent with high GSH and SOD levels we found in a study [40,41,38].

An active lifestyle is regarded as a major component of healthy ageing. Since RES was asserted to have a performance boosting impact in work out, it has been expected that RES may give maintaining health in maturing and expanding the quality of life [42,43]. During supramaximal anaerobic exercise, the expansion in the free radical generation is basically because of a dramatic increment in oxygen uptake. Short term supramaximal anaerobic exercise has been related to a substantial lactic acidosis in both blood and muscle and furthermore with a noteworthy increment in plasma catecholamine concentrations [44,45]. When ROS generation overwhelms the protection and repair systems, the net impact is oxidative stress and oxidative damage to DNA, layer lipids, and proteins [46,47].

In our study, show that acute swimming exercise was increased oxidative stress and DNA damage this these findings show that short-term supramaximal anaerobic exercise was produced free radicals and by depending on this situation was has emerged DNA damage.

Besides this study was show that the positive effect of resveratrol supplementation on the oxidative stress and oxidative DNA damage in acute swimming exercise.

In this examination, resveratrol was considered as a fairly antioxidant feature because it importantly diminished TOS levels, 8-OHdG levels and MDA levels. Moreover, it expanded antioxidant enzymes levels in the exhaustive exercise group. The results obtained from this experiment are compatible with previous studies about antioxidant activity of resveratrol [40,41].

The outcome obtained from this study guarantee the principal information about the effect of resveratrol supplementation on DNA damage utilizing comet assay on intense swimming activity rats. Also, resveratrol influences 8-OHdG levels by diminishing such levels in rats administered resveratrol compared with those intense exercise. Our results recommend that the diminishment in physical endurance induced by intermittent anaerobic swimming can be credited to lipid peroxidation, long enough rest intervals are necessary during anaerobic exercise to evade this reduction in physical endurance. In any case, the mechanisms by which antioxidant enzyme activity is increased are not known.

5. CONCLUSION

Outcomes of the study show that the increase in free radical production and DNA damage was because of acute swimming exercise in rats. Besides, Resveratrol has provided a longer swimming of rats in the exercise process. Resveratrol supplementation may be beneficial to promote the antioxidant system in heavy physical activity.

SIGNIFICANCE STATEMENT

Resveratrol is a capable antioxidant, and it can be utilized as a nutritious supplement by heavy athletes. It can be utilized as a strengthening agent for athletes. This examination has completed lacking in the literature.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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