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Effect of *Funalia trogii* in heart tissue of rats exposed to deltamethrin

[Deltametrine maruz kalan sıçanların kalp dokusunda *Funalia trogii*'nin etkisi]

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ABSTRACT

Objective: Environmental exposure to deltamethrin can cause alterations in structure and function of different organs. *F. Trogii,* a white-rot fungus, has antioxidative enzymes such as superoxide dismutase, catalase and glutathione reductase. It is hypothesized that there is an antioxidative role of *F. trogii* resulting in reducing the extent of heart injury as a result of oxidative stress. The aim of this study to investigate the effect of deltamethrin on heart and to evaluate possible protective role of *F. trogii* in alleviating the detrimental effect of deltamethrin on heart.

Materials and Methods: Twenty-one adult albino female Wistar rats were randomly divided into three groups of seven each: group 1 control, group 2 received deltamethrin, group 3 received deltamethrin plus *F. trogii* extract.

Results: The heart rate was increased and amplitude of QRS complex, duration of P wave and QRS complex were decreased due to deltamethrin administration. The superoxide dismutase and catalase activities were decreased, malondialdehyde level was increased in deltamethrin group. Ultrastructurally, dilatation in sarcoplasmic reticulum cisternaes and disorganisation in the myofibrils were observed in the deltamethrin group. In the deltamethrin plus *F. trogii* extract group, a decreasing lipid peroxidation and an increasing antioxidant enzyme activity, normal heart electrical activity and normal heart muscle structure was observed as similar to control group

Conclusion: *F. trogii* could protect against deltamethrin induced oxidative stress by decreasing lipid peroxidation and increasing superoxide dismutase and catalase activity. The results indicate the protective effect of *F. trogii* against heart injury and thereby support its traditional use.

Key Words: Antioxidant enzymes, deltamethrin, electrical activity, *Funalia trogii,* heart

Conflict of Interest: Authors declare no conflict of interest

ÖZET

Amaç: Deltametrinin çevresel maruziyeti farklı organların yapı ve fonksiyonunda değişikliklere neden olabilir. Beyaz çürükçül mantar *F. trogii* superoksid dismutaz, katalaz ve glutatyon redüktaz gibi antioksidan enzimlere sahiptir. *F. trogii'nin* sahip olduğu antioksidan rolünün oksidatif stresin neden olduğu hasarın derecesini kalp dokusunda da azaltacağı düşünülmektedir. Bu çalışmanın amacı deltametrinin kalp üzerine olan etkisini araştırmak ve deltametrinin kalp üzerine zararlı etkisini önlemede *F.trogii'nin* koruyucu rolünü değerlendirmektir.

Gereç ve Yöntemler: 21 adet erişkin albino dişi Wistar sıçanlar her grupta yedi adet olacak şekilde üç gruba ayrılmıştır: grup 1 kontrol grubu, grup 2'ye deltametrin, grup 3'e ise deltametrin ve *F. trogii* ekstraktı birlikte uygulanmıştır.

Bulgular: Deltametrin uygulanmasına bağlı olarak kalp hızı artmış, QRS kompleksinin genişliği, P dalga ve QRS kompleksinin süresi azalmıştır. Deltametrin grubunda superoksid dismutaz ve katalaz aktiviteleri azalmış, malondialdehit düzeyi ise artmıştır. Ultrayapısal olarak sarkoplazmik retikulum sisternalarında dilatasyon ve miyofibrillerde organizasyon bozukluğu gözlenmiştir. Deltametrin ve *F.trogii* ekstraktının birlikte verildiği grupta ise lipid peroksidasyonunda azalma, antioksidan enzim düzeylerinde artma ve kontrol grubuna benzer şekilde normal kalp elektriksel aktivitesi ve normal kalp ultrayapısı gözlenmiştir.

Sonuçlar: *F.trogii* lipid peroksidasyonunu azaltarak, superoksid dismutaz ve katalaz aktivitelerini arttırarak deltemetrinin neden olduğu oksidatif strese karşı koruyucu olabilir. Sonuçlar *F. trogii'nin* kalp hasarına karşı koruyucu etkisi olduğunu göstermekte ve dolayısıyla onun geleneksel kullanımını desteklemektedir.

Anahtar Kelimeler: Antioksidan enzimler, deltametrin, elektriksel aktivite, *Funalia trogii,* kalp

Çıkar Çatışması: Yazarlar arasında çıkar çatışması bulunmamaktadır.

Introduction

Pyrethroids are a class of synthetic potent neurotoxic compounds that are known to have high insecticidal activity, low toxicity in mammals, and they leave little residue in the biosphere [1]. They have been widely considered as ideal insecticides in agriculture, public health and veterinary applications on both farm animals and pets for the prevention and control of ectoparasites [2].

Pyrethroids prolong the opening of the voltage-sensitive sodium channel (VSSC) and raise a prolonged sodium tail current in mammalian as well as invertebrate neurons [3,4]. Furthermore, it has been reported that pyrethroids act on not only VSSC but also other ion channels or neurotransmitter receptors, such as voltage-gated chloride channels GABAA receptors and calcium channels [5].

Deltamethrin, a synthetic pyrethroid type II, is highly effective against a broad spectrum of insects [6-9].. However, like the other insecticides, deltamethrin affects non target organisms in addition to targets and causes genotoxic, immunotoxic and tumorogenic effects in mammalian and non-mammalian species [6,7].

Cardiovascular manifestations frequently accompany exposure to insecticides, which may be serious and are often fatal [10]. Like as other insecticides, pyrethroids may cause to cardiotoxic effects mediated by I_{Na} prolongation in cardiac myocytes [11]

Mushrooms have long been appreciated for their flavour and texture. They are recognized as a nutritious food as well as an important source of biologically active compounds of medicinal value. Modern clinical practice in Japan, China, Korea and other Asian countries relies on mushroom-derived preparations for therapy [12]. Medicinal effects have been demonstrated for many traditionally used mushrooms, including extracts of Favolus alveolarius [13], Phellinus linteus [14], Criolus versicolor [15]. Mushroom extracts can protect mammalian cells by possessing enzymes which deactivate compounds that can cause damage to cells. Our earlier study was reported the protective effects of cold buffer extract of F. trogii ATCC 200800 (FtE). We demonstrated antioxidant or free radical removing action of *F. trogii* extract [16].

The aim of this study to investigate the effect of deltamethrin on heart and to evaluate possible protective role of *F. trogii,* a white-rot fungus*,* in alleviating the detrimental effect of deltamethrin on heart.

Materials and Methods

Chemicals

The test compound deltamethrin (IUPAC: (S)-a-cyano-3-phenoxybenzyl (1R)-cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate; purity 98.0%) was obtained from Sigma-Aldrich Chemical Co. The LD_{50} of deltamethrin when given orally to rats was reported to be 128 mg/kg BW [17]. The tested dose of deltamethrin was 1.28 mg/kg BW (1/100 LD_{50}). Other chemicals and reagents were purchased from Sigma-Aldrich Chemical Co. and Merck. Wheat bran and soybean flour were supplied from a farm land.

Preparation of F. Trogii extract

Macrofungi *F. Trogii* was obtained from the Environmental Biotechnology Laboratory, Environmental Engineering Department, University of Mersin, Turkey. The fungi were maintained on potato Dextrose Agar (PDA; Merck) slants and incubated at 30ºC for 5 days and stored at 4ºC.

The solid-substrate fermentation (SSF) medium used for producing the fungal biomass consisted of wheat bran 36 g and soybean flour 4 g. The substrate was humidified with a 0.1 M, pH 6.0 sodium phosphate buffer added at 60 % v/w. The humidified medium was placed in one liter erlenmeyer flasks and autoclaved (120ºC, 60 min). The autoclaved medium was inoculated with the fungal stock cultures that had been grown on PDA. The flasks were incubated for 10 days at 30ºC and the contents were dried (Sanyo MIR 152 incubator) for 24 h at 40ºC. The dried material was ground in a coffee grinder for 2 min.

The ground biomass powder (1g) was suspended in potassium phosphate buffer (10 ml, 0.1 M, pH 6.0) for 15 min as described earlier [18]. Solids were removed by centrifugation at 12,000x*g* (Hettich Micro 22 R) for 15 min. The supernatant (i.e. the bioactive extract) was sterilized using a 0.22 μm fitler and diluted with aforementioned phosphate buffer to desired concentrations.

Specifications of F. trogii extract

Specification of *F. trogii* extract obtained after cold buffer extraction was reported by our earlier study *[16].* Same extract was used in this study. Specific activities (SA, unit enzyme activity/mg protein) of laccase and peroxidase enzymes were found 58 and 71, respectively. Protein and total phenol concentrations were calculated 2.53 mg and 26.30 μg in per ml of *F. trogii* extract *[16].*

Animals

Twenty-one adult albino male Wistar rats weighing 200-250 g were used in this study. The animals were acclimatized for a week to our laboratory conditions prior to experimental manipulation and were exposed to a 12-h light and 12-h dark cycle at a room temperature of 22ºC. They had free access to standard laboratory chow and water *ad libitum*. The rats were randomly divided into three groups as follows: (i) Group 1 (n=7): Control; (ii) Group 2 (n=7): Deltamethrin; (iii) Group 3 (n=7): Deltamethrin plus *F. trogii* extract.

Group 1 received only vehicle (corn oil; 0.5 ml), Group 2 received deltamethrin (1.28 mg/kg, bw, dissolved in 0.5

ml corn oil) and Group 3 received *F. trogii* extract plus deltamethrin dissolved in 0.5 ml corn oil. Deltamethrin and the fungi extract were applied at the same day. Rats were orally treated one dose per 48 h given in 30 days (total 15 doses/animal). The Institutional Animal Care and Use Committee at Mersin University Medical Faculty approved the experiments described in this study.

Electrical activity of the heart

The electrical activity of the heart was recorded using the BIOPAC MP 100 Acquisition System Version 3.5.7 (Santa Barbara, USA). Rats were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and (xylazine 10 mg/kg) and connected to a computerized electrocardiographic monitor. Then lead I electrodes were connected to an amplifier (BIOPAC ECG 100B) by a shielded three-electrode lead set. The signals were digitized with a 16-bit analog-to-digital converter at a sampling rate of 2500 samples/s. BIOPAC Acknowledge Analysis Software (ACK 100 W5.7 version) was used to measure the amplitude and duration of the P wave, QRS complex, and heart rate.

Biochemical assay

After excision, fresh heart samples were homogenized with 50 mM phosphate buffer (pH 7.4). Then homogenates were centrifuged at 10,000x*g* for 15 min at 4°C. Supernatants were separated and kept at -20°C until enzyme activity and malondialdehyde measurements were performed.

Heart malondialdehyde (MDA) level was determined by thiobarbituric acid (TBA) reaction according to the Yagi method [19]. This method relies on the measurement of the pink color produced by interaction of thiobarbituric acid with malondialdehyde elaborated as a result of lipid peroxidation. The colored reaction of 1, 1, 3, 3-tetraethoxypropane was used as the primary standard.

Tissue superoxide dismutase (SOD) activity was measured by the inhibition of nitroblue tetrazolium (NBT) reduction due to O_2^- generated by the xanthine/xanthine oxidase system according to Sun et al. [20]. One unit of SOD activity was defined as the amount of protein causing 50 % inhibition of the NBT reduction rate.

Catalase (CAT) activity of tissues was determined according to the method of Aebi et al. [21]. The enzymatic decomposition of hydrogen peroxide (H_2O_2) was followed directly by a decrease in absorbance at 240 nm. The difference in absorbance per unit time was used as a measure of CAT activity. The values were expressed as U/mg wet tissue weight.

Tissue protein content was determined according to the method developed by Lowry et al. [22] using bovine serum albumin as standard.

Histological evaluation

For electron microscopic investigations, heart samples were fixed with 2.5% glutaraldehyde, postfixed with 1% osmium tetroxide, dehydrated in graded alcohol series, cleared with propylene oxide and embedded in expoxy resin. Thin sections (50-70 nm) were cut by ultramicrotome (Leica UCT-125, Leica Microsystems GmbH, Wien, Austria) and contrasted with uranyl acetate and lead citrate. Sections were examined and photographed by an electron microscope (JEOL JEM-1011, Jeol Ltd., Tokyo, Japan).

Statistical Analysis

Statistical analysis was performed using a commercially available software (MedCalc v. 11.6.1). The Shapiro–Wilk test was used to check the normality of the distribution. The homogeneity of variance was determined using Levene test. The Kruskal-Wallis test was used for variance analysis and the statistical comparisons were performed by using Student Newman Keuls posthoc test. Descriptive statistics were used to establish the median and maximum-minimum values. Values of $p < 0.05$ were considered statistically significant.

Results

The heart rate and the amplitude, and duration of the P wave and QRS complex were recorded using an electrocardiogram. Statistically, the heart rate was significantly higher in the deltamethrin group than the control and deltamethrin plus *F. trogii* extract group ($p<0.05$). There was a significant reduction in the amplitude of the QRS complex in deltamethrin group compared with those of the control group and deltamethrin plus *F. trogii* extract group (Table 1). The duration of both P wave and QRS complex was significantly lower in the deltamethrin group than the control group and deltamethrin plus *F. trogii* extract group.

The levels of MDA were increased in deltamethrin and deltamethrin plus *F. trogii* extract groups compared with control ($p<0.05$). CAT activity significantly increased in deltamethrin plus *Funalia trogii* extract group as compared to control and deltamethrin groups ($p<0.05$) and it was significantly decreased in deltamethrin group when compared to control group. SOD activity significantly decreased ($p<0.05$) in deltamethrin group but significantly increased in deltamethrin plus *F. trogii* extract group ($p<0.05$) as compared to control group (Table 2).

Ultrastructurally, normal heart muscle characteristics were observed in the control group (Figure 1), while dilatation of sarcoplasmic reticulum cisternaes, and disorganization, thinning and breaking off in some myofibrils in the deltamethrin group were determined (Figure 2,3). However, in the deltamethrin plus *F. trogii* extract group, normal heart muscle structure was observed as similar to control group (Figure 4).

Table 1. The electrocardiogram analysis of the rats belonging to different experimental groups

Variables	Control		Deltamethrin		Deltamethrin plus *F. trogii* extract	
	Min-Max.	Median [% 25-75 percentils]	Min-Max.	Median [% 25-75 percentils]	Min-Max.	Median [% 25-75 percentils]
P wave amplitude (mV)	0.008-0.034	0.023 [0.012-0.028]	0.007-0.020	0.015 [0.009-0.018]	0.013-0.076	0.015 [0.014-0.053]
QRS amplitude (mV)	0.16-0.35	0.176 [0.165-0.328]	0.10-0.15	0.131 [0.115-0.146]*	0.097-0.26	0.151 [0.122-0.236]
P wave duration (s)	0.027-0.038	0.034 [0.030-0.038]	0.020-0.031	0.024 [0.021-0.029]*	0.027-0.041	0.031 [0.029-0.038]
QRS duration (s)	0.038-0.066	0.047 [0.040-0.058]	0.021-0.048	0.033 [0.023-0.043]*	0.031-0.055	0.041 [0.035-0.050]
Heart rate (beats/min)	280.10-361.44	308.51 [283.93-355.85]	353.98-413.79	365.34 [354.76-381.23]*	304.56-413.79	353.98 [325.69-384.41]

* Significant difference from control group and deltamethrin plus *F. trogii* extract group at $p<0.05$

Table 2. The levels of MDA, CAT and SOD in different groups of rats.

Variables	Control		Deltamethrin		Deltamethrin plus *F. trogii* extract	
	Min-Max.	Median [% 25-75 percentils]	Min-Max.	Median [% 25-75 percentils]	Min-Max.	Median [% 25-75 percentils]
CAT (U/mg protein)	2.22-4.43	3.27 [2.27-4.13]	1.25-2.80	1.74 [1.32-2.54]*	9.08-13.25	12.32 [10.04-12.89]*,†
SOD (U/mg protein)	3.52-5.47	4.38 [4.05-4.91]	1.61-2.83	2.22 [1.69-2.79]*	6.52-10.41	8.03 [7.22-9.45]*,†
MDA (nmol/mg protein)	0.16-0.30	0.20 [0.17-0.29]	0.79-0.95	0.88 [0.85-0.92]*	0.38-0.74	0.52 [0.43-0.68]*,†

*Significant difference from control group at $p<0.05$

†Significant differences from deltamethrin group at $p<0.05$
effect of deltamethrin in heart.

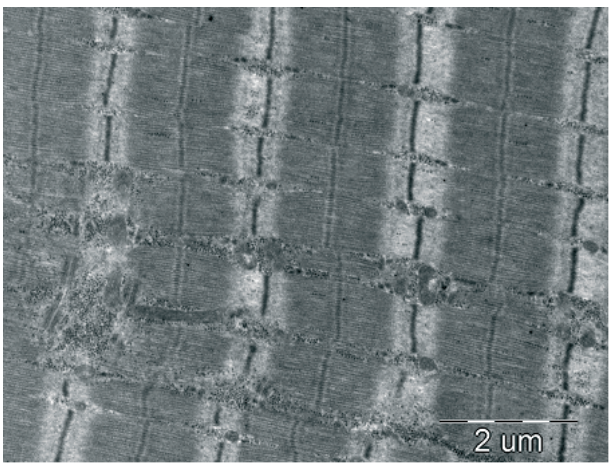

Figure 1. Electron micrographs of the heart tissue samples from control rats indicated a normal morphologic characteristic.

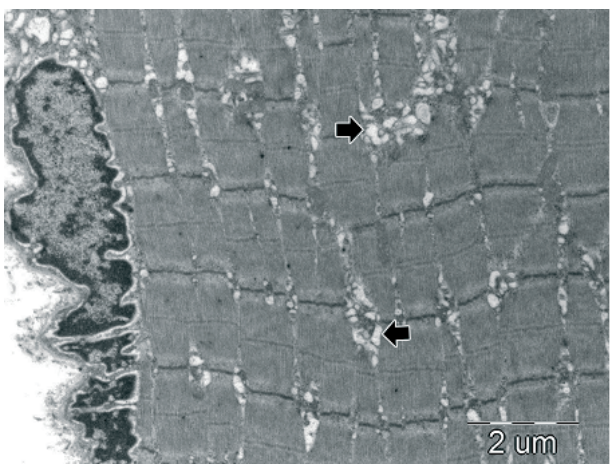

Figure 2. Representative micrograph of a dilatation sarcoplasmic reticulum cisternaes (arrow) in deltamethrin group.

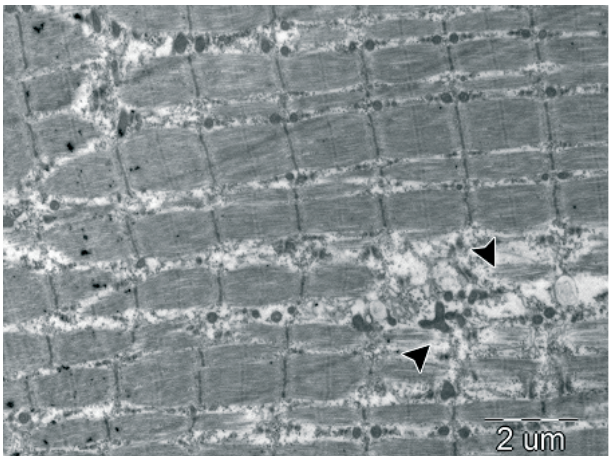

Figure 3. Degeneration in myofibrils (arrow head) was detected in the hearts of the rats in deltamethrin group.

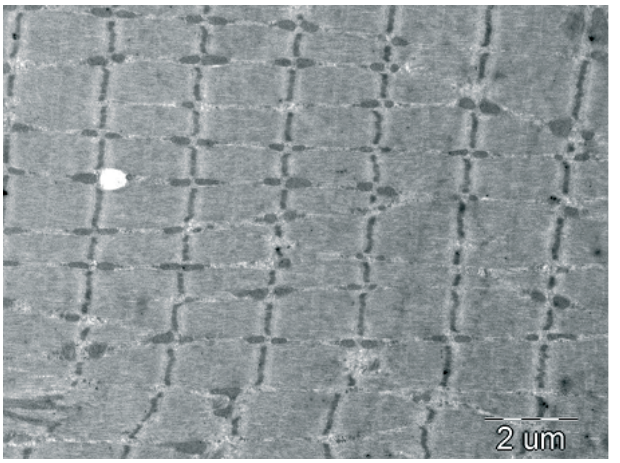

Figure 4. Normal heart muscle characteristics were observed in the heart samples of the rats in deltamethrin plus *F. trogii* extract group.

Discussion

Our study revealed that the presence of *F. trogii* extract could diminish the toxic effects of deltamethrin on rats heart.

Free radicals are continuously produced *in vivo* and can adversely alter lipids, proteins and DNA and have been implicated in aging and a number of human diseases [23]. Cells have different antioxidant systems including low molecular weight antioxidant molecules like glutathione [24] and various antioxidant enzymes to defend themselves against free radical attacks. SOD, the first lines of defence against oxygen-derived free radicals, catalyses the dismutation of the superoxide anion (O_2^-) into H_2O_2 that can, in turn, be transformed into H_2O and O_2 by CAT. There is some evidence to suggest that the antioxidant systems allow cells to undergo normal differentiation. Alterations in the enzymatic system, in particular, are believed to play a central role in this process [25]. Oxidative stress occurres as a consequence of imbalance between the production of free radicals and the antioxidative process in favor of radical production [26].

Recent studies indicate that pesticide intoxication produce oxidative stress by the generation of free radicals and induce tissue lipid peroxidation in mammals and other organisms [27-29]. In addition, free radicals have been shown to be key mediators of myocardial reperfusion injury and lipid peroxidation [30]. MDA is a major oxidation product of peroxidized polyunsaturated fatty acids and increased MDA content is an important indicator of lipid peroxidation. In the current study, MDA level was increased in deltamethrin treated rats. Some studies demonstrated that deltamethrin induced lipid peroxidation in fish and rats [31,32]. Moreover, treatment with deltamethrin depleted CAT and SOD activities of rats in our study. Possible reasons for the lowered CAT and SOD activities of heart tissues might be their utilization to challenge the prevailing oxidative stress under the influence of free radicals generated from deltamethrin and/or inhibition of enzyme synthesis by deltamethrin. Our results are in accordance with the findings obtained by Yousef et al. [32].

Health beneficial role of mushrooms as a biological response modifier, on the other hand, has attracted much attention because of their broad spectra of physiological activities including antitumor, immune-modulating, cholesterol-lowering, anti-inflammatory and antioxidant effects [12,33,34]. Enzymatic analysis showed that four important scavenger enzymes were found in F. trogii extract: SOD, ascorbate peroxidase (APX), CAT and glutathione reductase (GR) [18].

In this study, we confirmed antioxidant properties of the *F. trogii* extract in terms of their effect on parameters such as MDA concentration and the levels of CAT and SOD enzymes. Alterations of these parameters promoted the cardioprotective effects of *F. trogii* in rats receiving deltamethrin. The extract possibly confers this protective effect by dampening the generation of free radicals induced by deltamethrin.

Changes in the QRS complex of the rats ECG treated with the pesticides and the hearts voltage histopathology including the myofibrils number and arrangement might be explained by cell necrosis [35]. Necrosis occurs when cells are deprived of oxygen or energy, leading to the loss of cellular membrane integrity, the influx of extracellular fluid, cellular swelling, and the release of proteolytic enzymes that cause cellular disruption [35]. Lipid peroxidation could be the culprit in our setting for it can distrub cell membrane integrity and alter electrical activity of heart. In addition, we obtained a significant increase in the heart rate that could be due to weakening of the myocardium and an increase in sympathetic reflexes.

In conclusion, deltamethrin has a cardiotoxic effect on heart evidenced by an increasing lipid peroxidation, decreasing antioxidant enzyme activity, breaking heart

electrical activity and heart ultrastructure. However *F. trogii* could effectively ameliorate the deltamethrin induced oxidative stress. Consequently, supplementation of *F. trogii* may act as a protective agent against the toxic

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The authors declare no conflict of interest.

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