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Naringin is Protective in Paclitaxel-Induced Peripheral Neuropathy; A Multi-Biomarker Approach

Selçuk Yılmaz[1*], Hasan Şimşek[2], Sefa Küçükler[3], Serpil Aygörmez[4], Ender Erdoğan[3], Fatih Mehmet Kandemir[5]

[1]Department of Orthopaedics and Traumatology, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkey.
[2]Department of Physiology, Faculty of Medicine, Aksaray University, Aksaray, Turkey.
[3]Department of Biochemistry, Faculty of Veterinary, Atatürk University, Erzurum, Turkey.
[4]Department of Biochemistry, Faculty of Veterinary, Kafkas University, Kars, Turkey.
[5]Department of Medical Biochemistry, Faculty of Medicine, Aksaray University, Aksaray, Turkey.

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****Corresponding Author***
Selçuk Yılmaz
Department of Orthopaedics and Traumatology
Faculty of Medicine
Kütahya Health Sciences University
Kütahya, Turkey.
Phone: +90 5336651976
E-mail: dryilmazselcuk@gmail.com

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Authors' ORCIDs
Selçuk Yılmaz
http://orcid.org/0000-0003-2508-8558
Hasan Şimşek
http://orcid.org/0000-0001-5573-4923
Sefa Küçükler
http://orcid.org/0000-0002-8222-5515
Serpil Aygörmez
http://orcid.org/0000-0002-5675-5096
Ender Erdoğan
http://orcid.org/0000-0003-4360-6013
Fatih Mehmet Kandemir
http://orcid.org/0000-0002-8490-2479

Abstract: Cancer is a disease that is on the rise worldwide. Paclitaxel (PTX) is one of the most common chemotherapeutic agents used in the treatment of many cancers. PTX causes toxic effects by increasing oxidative stress in tissues. Naringin (NRG) is a powerful antioxidant found naturally in many plants, especially citrus fruits. The aim of this study was to determine the protective effects of NRG in PTX-induced sciatic nerve injury. Thirty-five male rats were randomly divided into five groups: control, PTX, NRG, PTX+NRG-50, and PTX+NRG-100. PTX was administered intraperitoneally (i.p.) for the first five days, and NRG 50 or 100 mg/kg orally on days 6-14. Sciatic nerve tissues were harvested and analyzed for markers of oxidative stress, inflammation and apoptosis damage levels by biochemical methods. PTX caused oxidative stress damage by increasing lipid peroxidation (MDA) and decreasing antioxidant capacity (SOD, CAT, GPx, and GSH), inflammatory damage by increasing proinflammatory cytokine (NF-κB, TNF-α, IL-1β, SIRT1, TLR4, and NRF2) release, apoptotic damage by increasing apoptotic factor (Bax) and decreasing antiapoptotic factor (Bcl-2) in sciatic nerve tissue ($p<0.05$). NRG, on the other hand, reversed all these changes in sciatic nerve tissue and reduced PTX-induced oxidative stress damage, inflammatory damage and apoptotic damage ($p<0.05$). These effects were more effective at the 100 mg/kg dose of NRG than at the 50 mg/kg dose ($p <0.05$). In sciatic nerve tissue, PTX induced peripheral neuropathy with increased oxidative stress, inflammation and apoptotic damage. NRG showed a protective effect against PTX-induced peripheral neuropathy. ©2023 NTMS.

Keywords: Apoptosis; Naringin; Oxidative stress; Paclitaxel; Sciatic nerve.

1. Introduction

According to 2020 global data, 19.3 million new cases and 10 million deaths were reported to be associated with cancer [1]. Different treatment options for cancer have been developed over the years. Cancer treatment

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includes surgery and various specific therapies such as radiation therapy, chemotherapy, immunotherapy, hormonal therapy, radiotherapy and targeted therapy [2]. When using chemotherapy to treat cancer, unexpected side effects such as peripheral neuropathy (PN) occur. Chemotrapotic agents such as taxanes cause the development of PN [3]. PN leads to dose restriction and even treatment cessation in patients during treatment. Therefore, this leads to a decrease in patients' quality of life and survival rates [4].

Paclitaxel (PTX) is an effective chemotherapeutic agent used to treat many cancers, such as ovarian, bladder, and other solid tumor cancers [5]. In clinical trials (phase I, II and III) from 1977 to 1992, taxol (commercial form PTX) proved to have a therapeutic effect on ovarian cancer, breast cancer, uterine cancer and other cancers. Taxol was the US Food and Drug Administration (FDA)-approved in 1992 for the therapy of certain cancers [6]. It is the most widely used and effective natural remedy among existing anti-cancer drugs due to its action by stopping cell growth, cycle, and division [7]. PN is one of the most common side effects, occurring in approximately 60% of patients receiving chemotherapy treatment. Almost all (97%) of all gynecologic and urologic cancer patients receiving PTX therapy develop PN [8].

Compounds found naturally in plants and fruits can provide benefits against unwanted harmful effects in organs and tissues due to their antioxidant effects [9]. Flavonoids, which are important components in many medicinal plants, are highly effective in maintaining tissue and body health. These activities include anti-cancer, anti-mitotic, antiproliferation, anti-apoptotic, and anti-oxidation properties [10, 11]. Naringin (NRG) is a naturally occurring and clinically proven flavone glycoside found primarily in grapefruit and citrus fruits. The average amount of NRG in grapefruit is around 17 mg/100 g [12]. NRG inhibits cyclo-oxygenase and 5-lipo-oxygenase pathways, which play a significant role in arachidonic acid metabolism, thereby eliminating free radicals, reducing lipid peroxidation and showing anti-inflammatory effects [13]. The current study aimed to determine the effects of NRG on oxidative stress, inflammation, and apoptosis damage parameters in PTX-induced PN, an anticancer agent with known toxic side effects.

2. Material and Methods

2.1. Chemicals

PTX was purchased from Koçak Pharmaceuticals (Taksen 300 mg/50 ml, Istanbul/Türkiye). NRG and all other chemicals (analytical purities) were obtained from Sigma Chemical Co. (St. Louis, USA).

2.2. Experimental Procedure

Thirty-five male rats (Sprague dawley, 220-250 g, 10-12 weeks) obtained from Atatürk University Experimental Animal Center (Erzurum, Türkiye) were used in the experiments. Rats were housed under standard laboratory conditions (12-h light and dark cycle, ventilation, 23±2°C, standard cage). Unlimited access to food and drinking water was provided. Rats were randomly divided into 5 groups (n=7). PTX and NRG doses were determined from the literature [3, 10].

1-Control (CNT): Saline was administered intraperitoneally (i.p.) 0.2 ml for the first five days and then orally on days 6-14.

2-Naringin (NRG): After 0.2 ml saline was administered i.p. for the first five days, NRG 100 mg/kg was administered orally on days 6-14.

3-Paclitaxel (PTX): For the first five days, 0.2 ml PTX (2 mg/kg) solution was administered i.p. followed by oral administration of 0.5 ml saline on days 6-14.

4-Paclitaxel+Naringin 50 (PTX+NRG-50): PTX was administered i.p. for the first five days, followed by NRG 50 mg/kg orally on days 6-14.

5-Paclitaxel+Naringin 100 (PTX+NRG-100): PTX was administered i.p. for the first five days, followed by NRG 100 mg/kg on days 6-14.

2.3. Collection of Samples

Twenty-four hours after the last administration of NRG (day 15), sciatic nerve tissue was removed. Sciatic nerve tissue was washed in physiologic saline and stored.

2.4. Lipid Peroxidation Analysis

To determine the malondialdehyde (MDA) level in sciatic nerve tissues, 532 nm absorbance was measured after reaction with thiobarbituric acid. For MDA analysis of sciatic nerve tissues, homogenization was performed according to the previous method [3]. For the analysis of MDA levels, the method in the literature was used [14].

2.5. Antioxidant Analysis

Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) activities and glutathione (GSH) levels were analyzed to analyze the antioxidant status of sciatic nerve tissue. Homogenization of sciatic nerve tissues for analysis of antioxidant markers was performed according to the previous method [9]. SOD [15], CAT [16], GPx [17], and GSH [18] were determined using the literature. Lowry et al. method was used for protein analysis [19].

2.6. Analysis of Inflammatory Markers

Cytokine production in sciatic nerve tissue was determined by ELISA using commercial kits by the procedure. Supernatants obtained from homogenates prepared with phosphate buffer (pH 7.4, 0.1 M) were used in the analysis. Nuclear Factor kappa B (NF-κB), Tumor necrosis factor alpha (TNF-α), Interleukin-1β (IL-1β), Sirtuin 1 (SIRT1), Toll-Like Receptor 4 (TLR4), and Nuclear factor erythroid 2-related factor 2 (NRF2) levels were determined from sciatic nerve tissue using a rat ELISA kit (Sunred, China).

2.7. Analysis of Apoptotic Markers

Supernatants obtained from homogenates prepared with phosphate buffer (pH 7.4, 0.1 M) were used for apoptotic damage level analysis in sciatic nerve tissue. Bax and B-cell lymphoma 2 (Bcl-2) levels were determined from sciatic nerve tissue using a rat ELISA kit (YL Biont, China).

2.8. Statistical Analysis

Statistical analysis of the data obtained from sciatic nerve tissues was performed with SPSS 20.0 (IBM, NY) program. One-way ANOVA and Tukey's post hoc tests were used for comparison between groups. Data are presented as Mean±SEM. Statistical significance was accepted: $p<0.05$.

3. Results

3.1. Oxidant and Antioxidant Status Findings

It was found that SOD, CAT and GPx were inhibited and antioxidant activity decreased by decreasing GSH in PTX compared to the control ($p<0.05$). In addition, lipid peroxidation was manifested by an increase in MDA ($p<0.05$). Antioxidant enzyme activities and GSH increased and MDA decreased in PTX+NRG-50 and PTX+NRG-100 compared to PTX ($p< 0.05$). NRG showed more pronounced effects at a dose of 100mg/kg ($p< 0.05$). (Figure 1).

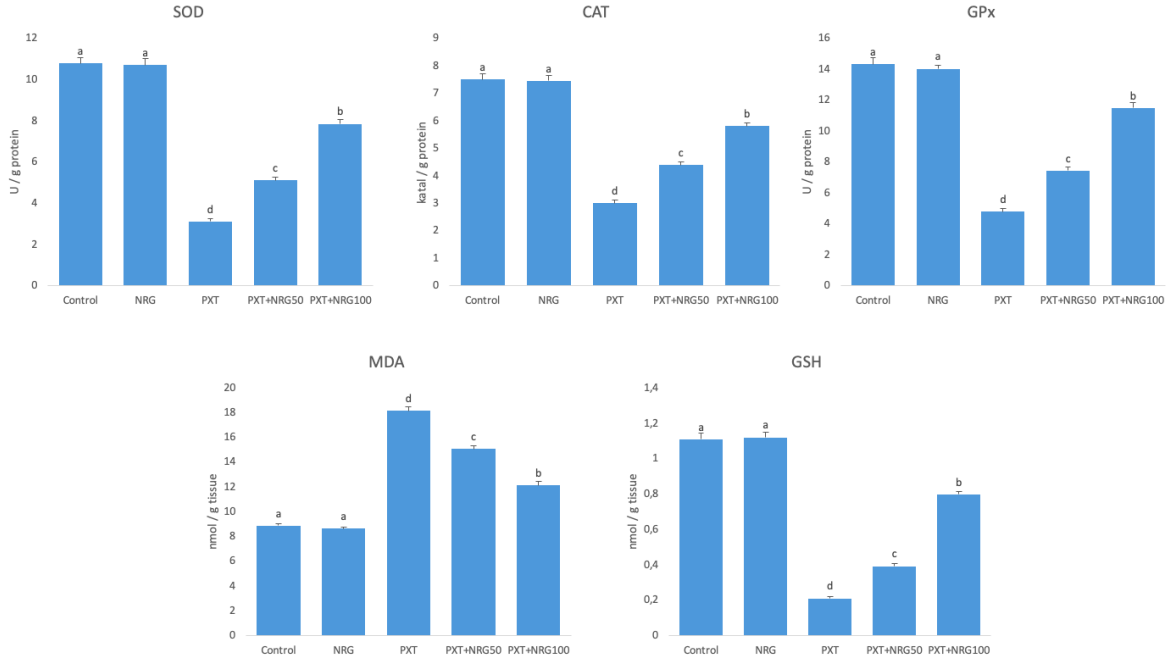

Figure 1: Effects of PTX and NRG administrations on oxidant and antioxidant markers in sciatic nerve tissues of rats. Values are given as Mean±SEM. Different letters indicate statistical difference: *$p<0.05$.

3.2. Inflammation Markers findings

Inflammation-related NF-κB, TNF-α, IL-1β, SIRT1, TLR4 and NRF2 in sciatic nerve tissues were analyzed by ELISA. There was an increase in NF-κB, TNF-α, IL-1β, SIRT1, TLR4 and NRF2 in the PTX compared to the control ($p<0.05$). PTX+NRG-50 and PTX+NRG-100 showed a decrease in all these parameters compared to PTX ($p<0.05$). When different doses of NRG were compared, 100 mg/kg was found to be more effective ($p< 0.05$) (Figure 2).

3.3. Apoptotic Markers Findings

In PTX, there was an increase in Bax ($p<0.05$) and a decrease in Bcl-2 ($p<0.05$). In PTX+NRG-50 and PTX+NRG-100, the changes in these parameters were reversed ($p<0.05$). NRG showed more pronounced effects at a dose of 100mg/kg (Figure 3).

4. Discussion

The taxane group of chemotherapeutics is a class of drugs commonly used in the treatment of many cancers. PTX is a taxane group chemotherapeutic that acts by inhibiting mitotic activity [20]. NRG is an active flavanone glycoside of grapefruit and various citrus plants with important biological effects such as antiulcer, antioxidant, anti-inflammatory, antiapoptotic and antihyperlipidemic [21, 22]. Therefore, in the current study, the effects of NRG on PTX-induced sciatic nerve tissue toxicity in rats were investigated.

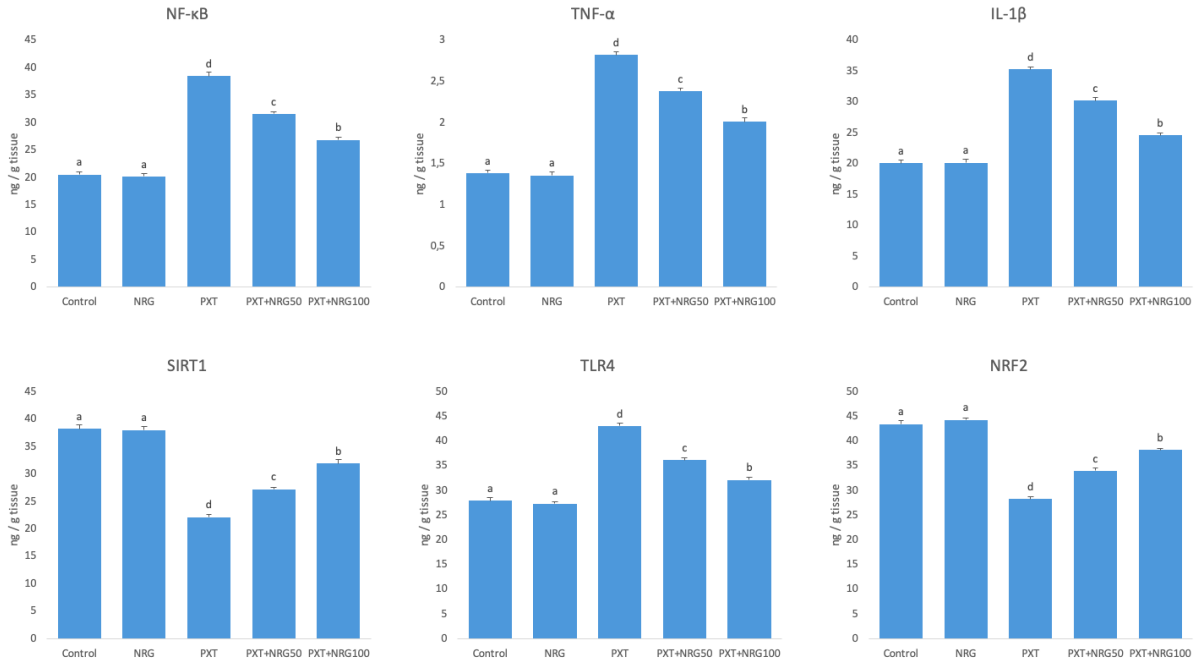

Figure 2: Effects of PTX and NRG administrations on NF-κB, TNF-α, IL-1β, SIRT1, TLR4 and NRF2 levels in sciatic nerve tissues of rats. Values are given as Mean±SEM. Different letters indicate statistical difference: *p<0.05.

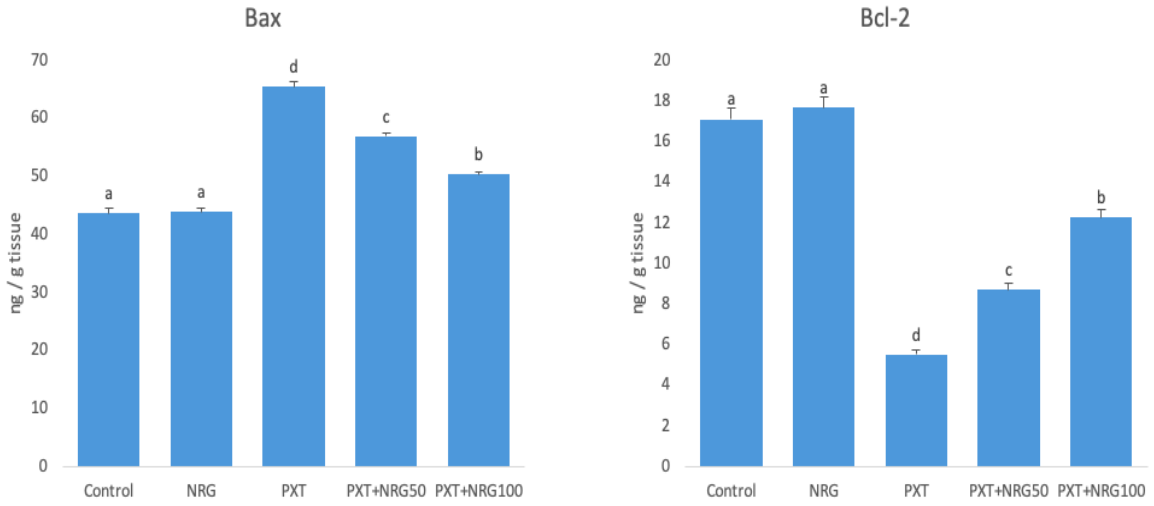

Figure 3: Effects of PTX and NRG administrations on Bax and Bcl-2 levels in sciatic nerve tissues of rats. Values are given as Mean±SEM. Different letters indicate statistical difference: *p<0.05.

ROS causes lipid peroxidation in cells and structural defects in proteins and nucleic acids [23]. Oxidative stress is an indicator of tissue damage characterized by an increase in ROS [24]. The end product of polyunsaturated fatty acid peroxidation is MDA [25]. GSH and GSH in tissues provide defense against ROS, highlighting their antioxidant and detoxification properties. GPx also contributes to antioxidant capacity by inhibiting lipid oxidation directly or indirectly together with GSH by reducing H_2O_2 [26]. Antioxidant enzymes contribute to cellular homeostasis by stabilizing ROS levels in healthy cells [27]. Antioxidant compounds are widely used to reduce the production and release of ROS [28]. In the current study, PTX increased oxidative stress by increasing MDA levels and decreasing antioxidant enzyme activities in sciatic nerve tissues. NRG administration, on the other hand, increased antioxidant activity by decreasing PTX-induced increased MDA levels and increasing antioxidant enzyme activities. This antioxidant activity was stronger, especially at 100 mg/kg.

Increasing evidence suggests that oxidative stress significantly triggers inflammation [29]. NF-κB is a transcription factor that is stimulated during inflammation in tissues and triggers the release of cytokines. With the activation of NF-kB, cytokines such as TNF-α and IL-1β are released and the inflammatory response is accelerated [30, 31]. In the current study, PTX caused inflammatory damage in sciatic nerve tissues by increasing NF-κB and related proinflammatory cytokines. NRG administration, on the other hand, reduced PTX-induced inflammatory damage by reducing NF-κB and related proinflammatory cytokines. NRG could emerge as an effective therapeutic agent in sciatic nerve tissue toxicity caused by inflammation due to PTX exposure.
Protective genes such as NRF2 are activated to protect against ROS-induced tissue damage. NRF2 is a redox-sensitive transcription factor that promotes transcription by binding to antioxidant response elements [32, 33]. NRF2 induction is a significant defense system in reducing damage against oxidative stress [34, 35]. There is growing evidence that TLR4 plays a pronociceptive role [36]. SIRT1, a histone deacetylase, is known to reduce neuropathic pain by activating NAD-dependent or NAD-independent pathways and inhibiting H4 acetylation. Activation of SIRT1 alleviates neuropathic pain [36]. In this study, PTX caused toxic damage to sciatic nerve tissues by increasing TLR4 and decreasing NRF2 and SIRT1. NRG administration reversed this situation and attenuated the damage.
Apoptosis (programmed cell death) is an essential physiological process that destroys and removes damaged or dangerous cells in the body [37, 38]. The increase of oxygen radicals negatively affects cellular activities related to intracellular signaling, such as the apoptotic pathway [39]. Bax and Bcl-2 play key roles in the mitochondrial pathway, an important pathway in apoptosis. As a result of the disrupted balance in the Bax/Bcl-2 ratio in favor of Bax, cytochrome c levels in the cytoplasm increase and enzymes that cause apoptosis such as Caspase-3 are activated [40]. In the current study, Bax levels, which is an apoptotic factor, increased with PTX exposure in sciatic nerve tissues, while Bcl-2, which is an antiapoptotic factor, decreased. When NRG was administered together with PTX, the opposite effect was observed and NRG exhibited antiapoptotic properties. Therefore, NRG may be an effective agent against apoptosis in PTX-induced sciatic nerve tissue toxicity.

5. Conclusions

In conclusion, PTX caused toxic effects by increasing inflammation, oxidative stress, and apoptosis damage levels in sciatic nerve tissue. On the other hand, NRG was found to reduce the toxic effect by decreasing all these damages. It can be concluded that administration of NRG, especially at 100mg/kg, would be much more effective in preventing sciatic nerve tissue damage in terms of all these pathways. We anticipate that NRG will increasingly come to the forefront of studies due to its powerful antioxidant properties and its inclusion in foods that are easily accessible in our daily diet. On the other hand, we anticipate that it will be effective in reducing the side effects of significant chemotherapeutic agents such as PTX used to treat cancer diseases, which are increasing worldwide, and in improving the quality of life of patients.

Limitations of the Study

The limitation of this study is that motor balance and coordination tests of rats could not be performed due to the lack of relevant devices.

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Conflict of Interests
There is no conflict of interest.
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This study received no financial support.
Author Contributions
SY and FMK designed the research. SY, HŞ, SK, SA, EE and FMK participated in data collection and data analysis. SY and HŞ wrote the manuscript, read and approved the final script.
Ethical Approval
The study was approved by Erzurum Atatürk University Experimental Animal Ethics Committee (2023/07-113).
Data sharing statement
None.
Consent to participate
None applicable.
Informed Statement
None.

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