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ORIGINAL ARTICLE

# The effect of tropisetron on peripheral diabetic neuropathy: possible protective actions against inflammation and apoptosis

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## Abstract

Diabetic peripheral neuropathy (DPN) is a common nerve disorder of diabetes. The aim of this study was to explore the protective effects of tropisetron in DPN. Type 1 diabetes was created by a single injection of streptozotocin (50 mg/kg, ip). Tropisetron (3 mg/kg, ip) was administered daily for 2 weeks. Our analysis showed that nerve fibers and their myelin sheaths were thinned with decreased myelinated fiber number in diabetic animals. The intensity of Bcl-2 staining decreased and the intensity of Bax staining increased in the sciatic nerves of diabetic rats by using immunohistochemical staining. Furthermore, diabetes significantly increased tumor necrosis factor-alpha, interleukin 1-β (TNFα and IL-1β) and Bax/Bcl-2 ratio in sciatic nerves of rats. However, intraperitoneal injection of tropisetron significantly reversed these alterations induced by diabetes. These findings suggest that tropisetron attenuates diabetes-induced peripheral nerve injury through its anti-inflammatory and anti-apoptotic effects, and may provide a novel therapeutic strategy to ameliorate the process of peripheral neuropathy in diabetes.

**Keywords** Diabetes · Sciatic injury · Tropisetron · Inflammation · Apoptosis

## Introduction

Diabetic peripheral neuropathy (DPN) is a serious chronic complication of diabetes (Shi et al. 2013). As a hallmark of diabetes, hyperglycemia can activate the polyol pathway which induces the accumulation of toxic metabolites in nervous tissues contributing to metabolic stress to the axon (Lós et al. 2019). Therefore, structural and functional impairment to peripheral nerves appears and causes neuronal disability through axonal atrophy, myelin sheath damage, and progressive nerve fiber loss (Ma et al. 2016).

Oxidative stress and inflammation are the most common pathological processes mediating diabetic complications, including DPN (Mirzakhani et al. 2018). Glucose neurotoxicity increases the expression of central inflammatory cytokines, such as TNFα and IL-1β, and leads to activation of the NF-kB pathway and, subsequently, apoptosis signaling and axonal degeneration (Dhaliwal et al. 2020,Lós et al. 2019,Ni et al. 2017).

Although insulin therapy is the standard method for type-1 diabetes mellitus (T1DM) treatment, it does not stop the several complications of DPN. Thus, there is a dire need to find an effective therapy for nerve damage in DPN.

Tropisetron, an antagonist of serotonin type 3 receptors, is extensively used as a safe antiemetic drug in chemotherapy (Barzegar-Fallah et al. 2014). Previous studies indicate that tropisetron exerts neuroprotective and anti-nociceptive effects in peripheral neuropathy models (Akada et al. 2006,Barzegar-Fallah et al. 2014).

The significant anti-diabetic activity of tropisetron via increasing GLUT2 gene expression and beta-cell mass in pancreatic tissue has recently been reported (Naderi et al. 2020b). Furthermore, tropisetron has been shown to suppress oxidative stress, pro-inflammatory cytokines, and apoptotic index in the pancreatic beta cells of diabetic rats (Naderi et al. 2020a, b).

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Tropisetron also exerts its therapeutic effects against some diabetic tissues such as the kidney (Barzegar-Fallah et al. 2015), liver (Amini et al. 2020), and myocardial cells (Asadi et al. 2016). Swartz et al. reported that tropisetron has neuroprotective effects on glutamate-induced excitotoxicity in the central nervous system (Swartz et al. 2013). Tropisetron also managed to suppress vincristine-induced neurotoxicity by an anti-inflammatory mechanism (Barzegar-Fallah et al. 2014). However, there is no information on diabetic peripheral neuropathy after tropisetron treatment. Thus, herein, we decided to explore the effects of intraperitoneal injection of tropisetron on sciatic nerve damage in diabetic conditions.

## Materials and methods

### Experimental protocol

Twenty one male Wistar rats 250 ± 20 g weight, 3–4 months old) were kept in cages with a 12-h light/12-h dark cycle at room temperature (21 ± 2 °C) and had ad libitum access to food and water. All the experimental protocols were approved by the Ethics Committee of Urmia University of Medical Sciences (Ethical Code: IR.UMSU.REC.1398.305). Due to the mortality rate of diabetes, at first we considered 10 animals in diabetic groups, but finally 7 animals data were analyzed in the study. The rats were divided into three groups ($n = 7$): control (normal saline, daily), diabetes (STZ, 50 mg/kg as a single dose, intraperitoneally, freshly dissolved in normal saline) (Naderi et al. 2020b) , tropisetron + diabetes (STZ + 3 mg/kg tropisetron, daily for 2 weeks, intraperitoneally dissolved in normal saline) (Barzegar-Fallah et al. 2015,Naderi et al. 2020b).

The diabetes induced in rats after an overnight fast. After 72 h of STZ injection, FBS were measured by a standard digital glucometer (Elegance, CT-X10, Frankenberg, Germany), then diabetes is diagnosed at fasting blood glucose (FBS) ≥ 300mg/dl in each rat. After diabetes established, rats treated with tropiseton for 2 weeks according to the animal's weight every day. Then, the animals euthanized with pentobarbital sodium (35 mg/kg, i.p.), (Sigma-Aldrich, Steinheim, Germany) and sciatic nerve dissected for later measurements.

### FBS measurement

At the end of 2 weeks, blood samples were obtained from the tip of the tail, and glucose levels were measured by using a digital glucometer (Elegance, CT-X10, Frankenberg, Germany).

### Preparation of sciatic nerve tissue for Luxol fast blue and immunohistochemical staining

After isolating sciatic nerves, apiece of this tissue was fixed with 10% formaldehyde. Then the samples were dehydrated and subsequently embedded in paraffin. Paraffin sections at 5-µm thick were prepared to evaluate the neuronal damage and myelination status by using Luxol fast blue staining. Myelin is stained blue, while axons remain white with Luxol fast blue staining. Myelin appeared as regular shapes, with a uniform thickness and clear boundary surrounding the myelin in healthy control group. By contrast, the myelin exhibited the worst fiber status and degeneration as evidenced by reduced myelin sheath thickness or loss of some myelinated nerve fibers leads to some disconnections after damage (Emir et al. 2016,Liu et al. 2016,Mustapha et al. 2019,Shi et al. 2013). The myelinated fiber number per 1 $mm^2$, axone diameter, and myelin thickness of the nervous were analyzed using a histomorphometric lens (Olympus, HHA) under 400 × magnification and software (ImageJ software, National Institutes of Health, USA).

The expression of BAX and BCL2 were examined by immunohistochemistry. For this purpose, the cross-sections were prepared; three sections from each sciatic/rat (in total 18 cross-sections/group) were stained. Mean distributions of Bcl-2+ and Bax+ cells were examined. In brief, the histological sections were heated at 56 °C for 25 min, de-paraffinized in xylene (2⨳), and subsequently rehydrated through a series of graded alcohol concentrations (each for 5 min). The retrieval process for antigens was conducted by using 10 mM sodium citrate buffer (pH: 7.2), followed by blocking endogenous peroxidases using 1.5% hydrogen peroxide in 1× phosphate buffer (PBS, 20 min at room temperature), and incubated in a superblock solution (SCYTEK Co., AA025, Utah, USA, Lot: 43961) for 10 min. The control (with no primary antibody) and the experimental slides were incubated overnight (4 °C), respectively, with the blocking solution alone or primary antibodies: Bcl-2 (1:100, Cat N: E-AB-60788) and Bax (1:100, Cat N: EAB-13814, Elabsciences, USA. Subsequently, incubated with peroxidase/HRP conjugated goat anti-rabbit IgG secondary antibody (1:500, Elabscienece, USA, Cat N: E-AB1003) for 60 min at laboratory temperature. Finally, the slides were incubated with a standard 3,3′-diaminobenzidine chromogen solution (DAB; Sigma, St. Louis MO) for 5 min to visualize the labeled proteins and then counterstained with hematoxylin for 10 s. Moreover, the pixel-based intensity of brown reactions, defining the target proteins, was assessed by software (ImageJ software, National Institutes of Health, USA) at 2540 µm × 2540 µm of a cross-section from each animal. For this

aim, images (20 megapixels) were captured by the onboard camera (Zeiss, Cyber-Shot, Japan). Next, the mean of pixel-based intensities of 3 images from one cross-section (in total 18 sections/each group) were examined, and the results were compared between groups. The normal IgG instead of primary antibody was used for negative control and positive control is healthy control rats (Shi et al. 2013).

### Western blotting

IL-1β, TNFα, Bax, and Bcl-2 protein levels in the sciatic nerve were determined by Western immunoblotting according to the method as indicated in our previous study (Naderi et al. 2020b). In brief, another part of sciatic nerve was isolated and homogenized and then sonicated in the buffer containing 1% Triton X-100, 0.1% sodium dodecyl sulfate (SDS), 50 mM Tris hydrochloride (Tris-HCl), pH 7.5, 0.3 M sucrose, 5 mM ethylenediaminetetraacetic acid (EDTA), 2 mM sodium pyrophosphate, 1 mM sodium orthovanadate, and 1 mM phenylmethylsulfonyl fluoride, supplemented with a complete protease inhibitor cocktail. The samples were centrifuged (15 min at 1000 × g at 4 °C) to produce the supernatant, and then proteins were isolated through the SDS-PAGE and electrotransferred to the nitrocellulose membrane. After blocking, anti-IL-1β, anti-TNFα, anti-Bax, and anti-Bcl-2 antibodies were utilized. The concentration of the proteins was determined, and immunoreaction density was evaluated using the ImageJ software. Catalog numbers and companies of antibodies are presented in Table 1.

### Statistical analysis

The data were expressed as mean ± SEM, and analyses were performed using SPSS 16.0. All the parameters were checked for normality using the one-sample Kolmogorov-Smirnov test. Data were statistically evaluated using one-way analysis of variance (ANOVA) followed by Tukey's test. The significant level was expressed at $P < 0.05$.

**Table 1** The antibodies used in Western blotting assays

| Primary antibody | Company | Dilution | Catalog number |
|---|---|---|---|
| IL-1β | Santa Cruz | 1:500 | sc-32294 |
| TNFα | Santa Cruz | 1:500 | sc-130349 |
| Bax | Santa Cruz | 1:500 | sc-7480 |
| Bcl2 | Santa Cruz | 1:500 | sc-492 |
| β-Actin | Santa Cruz | 1:300 | sc-47778 |

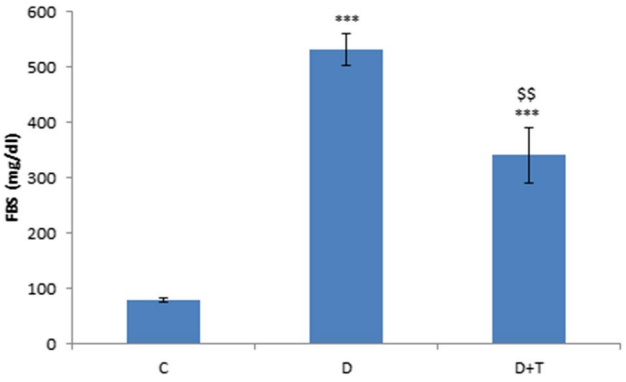


**Fig. 1** FBS level in different groups. ***$P < 0.001$, compared with control group. $^{\$\$}P < 0.01$, compared with diabetic group. Control (C); diabetes (D); and diabetes + tropisetron (D + T)

## Results

### Tropisetron decreased blood glucose level (mg/dl)

As shown in Fig. 1, blood glucose level increased significantly ($P < 0.001$) at the end of the experiment in the diabetic group compared to the control group. However, after 2 weeks of treatment, tropisetron usage could attenuate blood glucose level markedly ($P < 0.01$) in diabetic rats.

### Tropisetron ameliorated pathological changes of diabetic peripheral neuropathy

To examine the changes of axonal structure, Luxol fast blue staining of rat sciatic nerve was performed (Fig. 2). The axonal architecture in the sciatic nerves of the control rats was found normal. As shown in Table 2, some nerve fibers in the sciatic nerves of the diabetic group were thinned (7.849 ± 0.28) ($P < 0.01$) with decreased myelinated fiber number (73.13±3.03) ($P < 0.05$) compared to control group. In addition, myelin was degenerated leading to a reduced myelin sheath thickness (1.5 ± 0.3) in diabetic animals ($P < 0.05$). Tropisetron treatment mitigated these changes. Axon shrinkage (9.82 ± 0.44), myelinated fiber number (108 ± 5.01), and myelin thickness (3.8 ± 0.4) were improved partially by tropisetron treatment ($P < 0.01$). We further investigated the role of tropisetron in the intrinsic apoptotic signaling cascade which is called mitochondria apoptotic pathway. This pathway has been assumed to be critical in regulating apoptosis. The Bax and Bcl2 expression was evaluated by the immunohistochemistry in the sciatic nerve. Anti-apoptotic protein Bcl-2 as a key member in the Bcl-2 family, inhibits apoptosis; however, pro-apoptotic protein Bax could stimulate apoptosis. The diabetic rats showed strong positive staining for Bax (1.9 ± 0.4) and negative

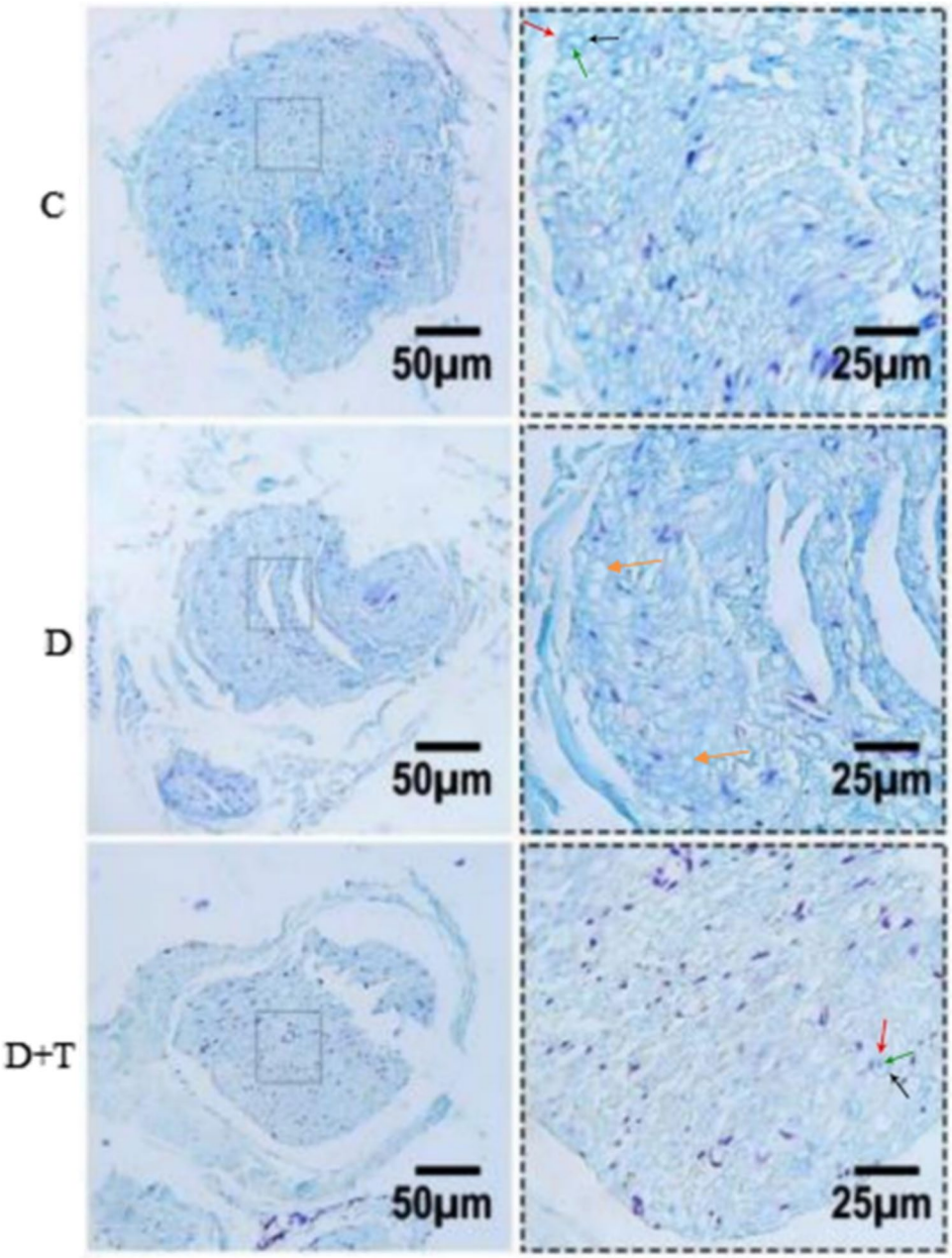


**Fig. 2** Histological examination of Luxol fast blue stained sciatic nerve in control (C); diabetes (D); and diabetes + tropisetron (D + T) groups. Scale bars are as indicated. Magnification = 100× and 400×. Myelinated fiber (red arrow), axon (green arrow), myelin sheath (black arrow), myelin degeneration (orange arrow)

**Table 2** Myelinated fiber number (n/mm$^2$), axon diameter (µm), and myelin thickness (µm) in different groups

| | Myelinated fiber number (n/mm$^2$) | Axon diameter (µm) | Myelin thickness (µm) |
|---|---|---|---|
| C | 95.8 ± 8.04 | 10.06 ± 0.25 | 3.8 ± 0.3 |
| D | 73.13 ± 3.03* | 7.849 ± 0.28** | 1.5 ± 0.3** |
| D + T | 108 ± 5.01$$ | 9.82 ± 0.44$$ | 3.8 ± 0.4$$ |

All the data are represented as mean ± SEM ($n = 7$): *$P < 0.01$, **$P < 0.01$, compared with control group. $^{\$\$}P < 0.01$, compared with diabetic group. Control (C); diabetes (D); and diabetes + tropisetron (D + T)

staining for Bcl2 (0.23 ± 0.11) in the sciatic nerve ($P < 0.05$), whereas the expression of Bax (0.95 ± 0.1) ($P < 0.05$) and Bcl2 (1.76 ± 0.35) ($P < 0.001$) in tropisetron-treated rats were lower and higher, respectively, as compared with the diabetic group (Fig. 3a-d), indicating a protective effect of tropisetron treatment in diabetic neuropathy.

## Tropisetron decreased TNFα, IL-1B, and Bax/Bcl-2 ratio in the sciatic nerve of STZ-induced diabetic rats

Cytokines can trigger inflammatory cascade contribute to severe diabetic neuropathy. For evaluation, the protein

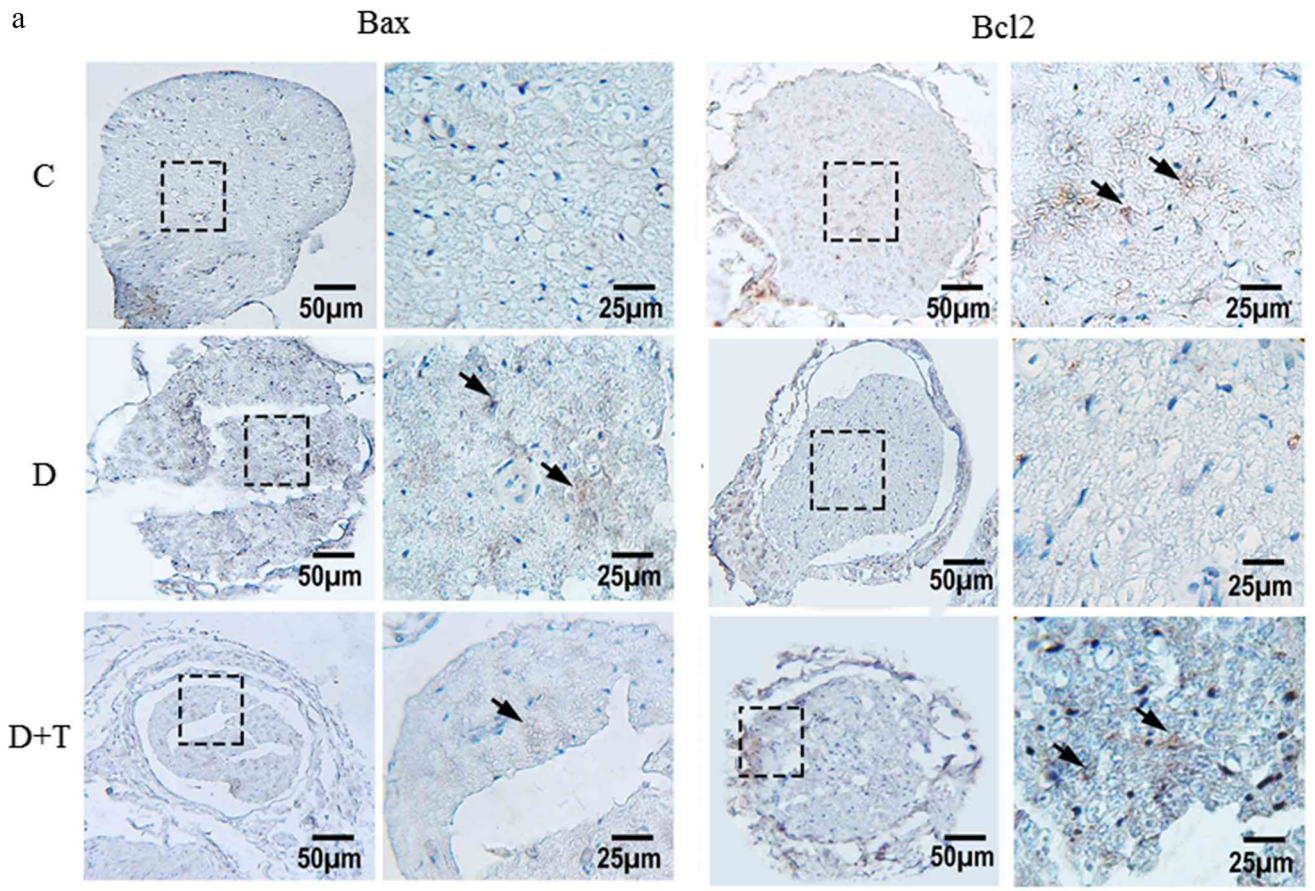


**Fig. 3** **a** Immunohistochemical staining for Bax and Bcl2 in control (C); diabetes (D); and diabetes + tropisetron (D + T) groups (brown arrows). (**b**, **c**) Quantitative Bax and Bcl2 intensity of the sciatic nerve; (**d**) software analysis for Bax and Bcl2 intensity in 2530 × 2530 μm of tissue. All the data are represented as mean ± SEM, $^{*}P < 0.05$, compared with the control group. $^{\$}P < 0.05$, $^{\$\$\$}P < 0.001$, compared with the diabetes group. Scale bars are as indicated. Magnification = 300×

levels of IL-1β and TNFα as main cytokines in the sciatic nerve, Western blotting was used in different groups. The data analysis presented a significant increase in TNFα (3.25 ± 0.44) and IL-1β (3.66 ± 0.14) protein levels in the diabetic group in comparison with the control group ($P < 0.001$) (Fig. 4a-c). We analyzed the expression of Bax and Bcl-2 in the sciatic nerve tissue. Anti-apoptotic protein Bcl-2 as an important member in the Bcl-2 family mitigates apoptosis; however, pro-apoptotic protein Bax could stimulate apoptosis. As shown in Fig. 4a and d, Bax protein expression increased and Bcl-2 protein expression decreased in the sciatic nerves of the diabetic animals. So, the Bax/Bcl-2 ratio was increased (4.58 ± 0.86) in the diabetic rats compared to the control group (0.98 ± 0.03) ($P < 0.001$). However, tropisetron treatment decreased IL-1β (1.99 ± 0.32), TNFα (1.18 ± 0.11) ($P < 0.001$), and the Bax/Bcl-2 ratio (1.68 ± 0.23) ($P < 0.01$) in the sciatic nerve of the diabetic animals (Fig. 4a-d).

## Discussion

Currently, there is no effective treatment except aggressive glycemic control in preventing or halting the development of diabetic neuropathy (Dhaliwal et al. 2020). As previously stated, tropisetron is a 5-HT3R antagonist which has been reported to exhibit remarkable antioxidant, anti-inflammatory, and anti-hyperglycemic effects (Barzegar-Fallah et al. 2014). Recently, we demonstrated in our previous study that tropisetron-ameliorated hyperglycemia and body weight loss in the diabetic animals (Amini et al. 2020). Moreover, it has shown to be particularly effective against various diabetic complications (Asadi et al. 2016,Barzegar-Fallah et al. 2015,Barzegar-Fallah et al. 2014). Based on this, in the present study, we aimed to investigate the protective effects of tropisetron against experimentally induced peripheral neuropathy in diabetic rats.

This study reported for the first time that tropisetron treatment can protect peripheral nerve tissue against

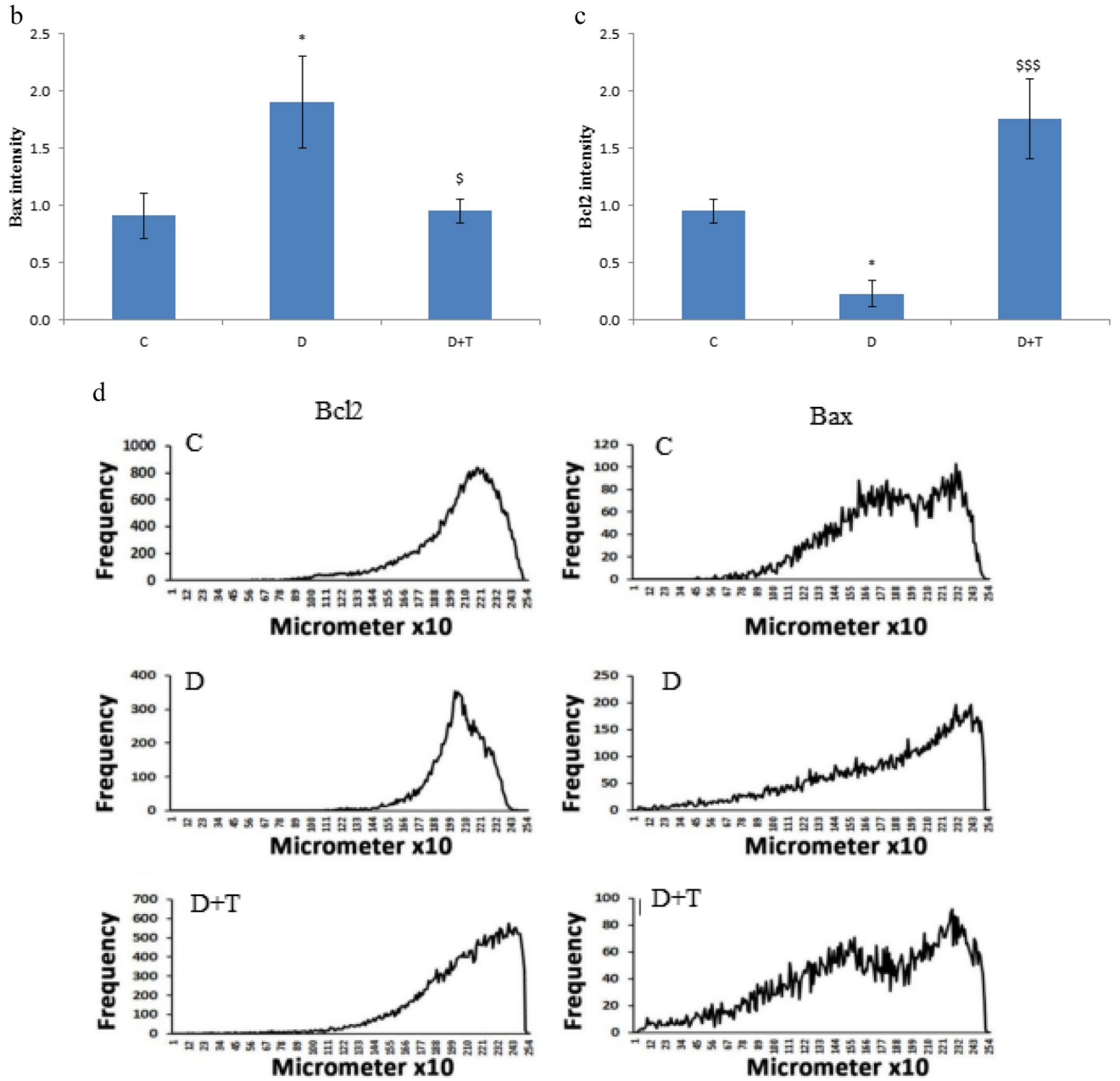


**Fig. 3** (continued)

STZ-induced damages via anti-inflammatory and anti-apoptotic effects. Tropisetron-treated diabetic animals exhibited a low level of TNFα, IL-1β, Bax, and a high level of BCL2 expression.

It is well known that increasing blood glucose level in diabetes promotes glucose influx to neurons and leads to the accumulation of glycolysis products (Thornalley 2002). It can cause multiple organ dysfunction and structural changes, e.g., in the peripheral nervous system. Small fiber neuropathy, myelin fibers' reduction, and axon loss in peripheral nerves may occur in high-glucose conditions (Sharma et al. 1981,Yagihashi et al. 1990). Therefore, the direct toxic effect of hyperglycemia, axon sheath abnormalities, and low blood flow are the major causes of pathophysiological alterations in diabetic neuropathy (Boulton and Malik 1998).

In agreement with previous studies (Erbaş et al. 2016, Liu et al. 2016), our histological analysis showed that the experimentally induced diabetes significantly reduced the density of myelinated fibers and myelin sheath thickness, as well as axonal thinning. Peng et al. declared that the morphology of the sciatic nerves showed signs of abnormality in the early

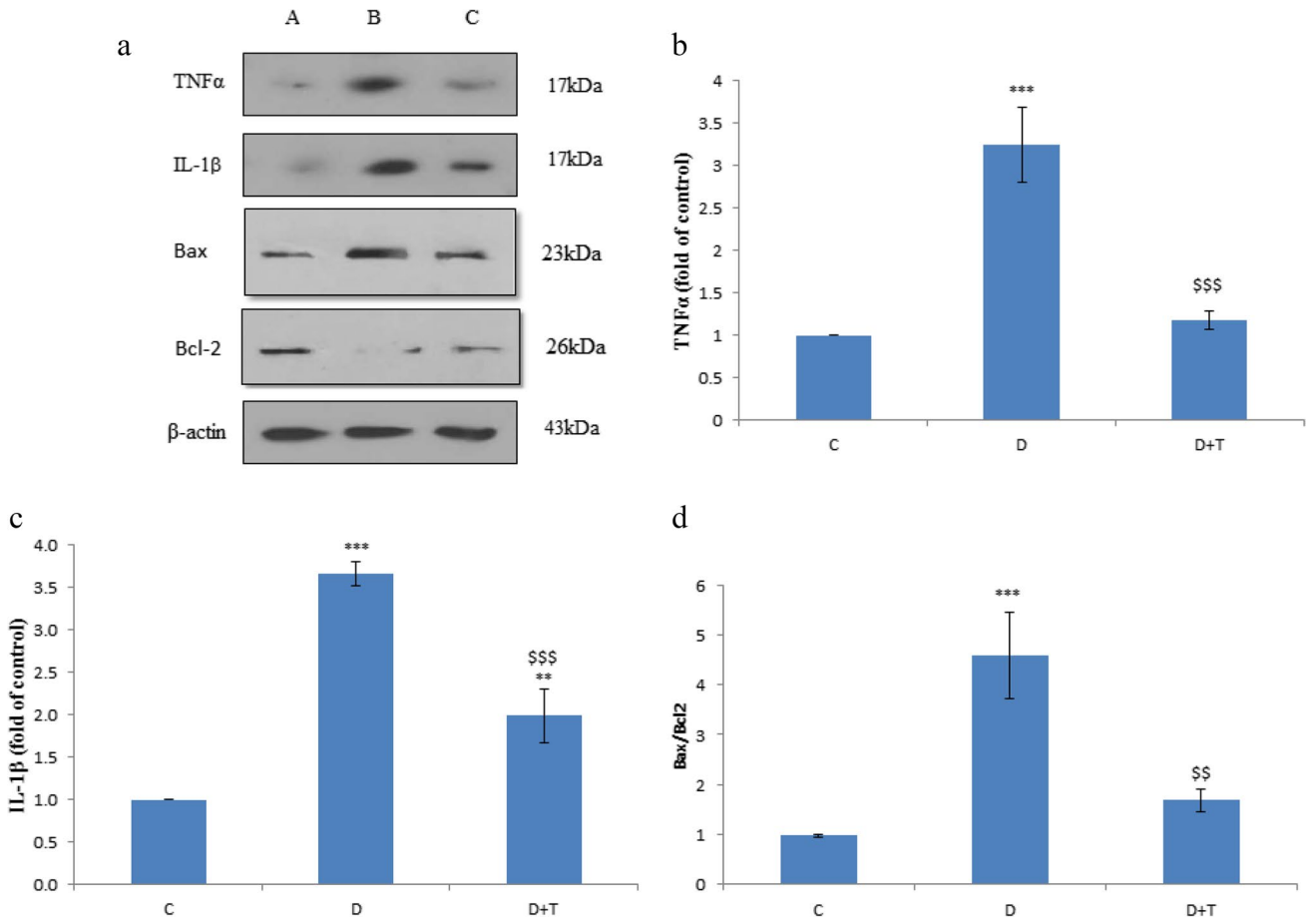


**Fig. 4** Evaluation of proinflammatory cytokines (TNFα and IL-1β) and Bax/Bcl-2 ratio in the sciatic nerves of different groups. (**a**) The blotting images of TNFα, IL-1β, Bax, and Bcl2; (**b**, **c**, **d**) The bar charts represent the quantitative analysis of TNFα, IL-1β, Bax/Bcl-2 ratio normalized against β-actin. $^{**}P < 0.01$, $^{***}P < 0.001$, compared with control group. $^{\$\$}P < 0.01$, $^{\$\$\$}P < 0.001$, compared with diabetic group. Control (C); diabetes (D); and diabetes + tropisetron (D + T)

stage of streptozotocin-induced diabetes in rats (Peng et al. 2015). Furthermore, some studies reported that the diabetic group showed a moderate irregular arrangement of nerve fibers after 2 weeks of diabetes induction (Moustafa et al. 2018a, b). However, in the present study, administrating tropisetron diminished the experimental diabetes-induced nerve damage and ameliorated the morphological characteristic of the peripheral nervous systems.

The mechanisms underlying the pathogenesis of DPN have not yet been fully established. Various reports have shown that inflammatory cytokines may play a key role in the development of DPN (Satoh et al. 2003). Long-lasting hyperglycemia can activate immune cells such as macrophages, neutrophils, and glial cells (Abcouwer 2011), thereby producing TNFα, IL-1β, and IL-6 levels (Shi et al. 2013). Pro-inflammatory cytokines can increase nerve excitability and myelin disturbances that contribute to nerve demyelination and inhibition cell survival (Alexandraki et al. 2008,Stettner et al. 2011). The anti-inflammation and neuroprotection effects of tropisetron were reviewed in ameliorating neurodegenerative diseases, including Alzheimer's, multiple sclerosis, and stroke (Fakhfouri et al. 2015). In the present study, we demonstrated a marked reduction in pro-inflammatory cytokines, including IL-1β and TNFα, in the sciatic nerve of neuropathic rats following tropisetron treatment.

Similarly, in a model of vincristine-induced neuropathy, rats treated with tropisetron presented improvement in nerve injury in a receptor-independent manner (Barzegar-Fallah et al. 2014). The anti-inflammation effect of tropisetron was confirmed in colitis (Utsumi et al. 2016). Yu et al. (Yu et al. 2018) showed that tropisetron attenuated lipopolysaccharide-induced neuroinflammation in the mouse cerebral cortex. Several in vivo and in vitro studies have described the anti-apoptotic effect of tropisetron in various conditions. Aminzadeh reported that tropisetron improved the viability of cells and protected them from hyperglycemia-induced apoptosis by modulating Bax and BCL2 protein expressions

in rat pheochromocytoma (PC12) cells (Aminzadeh 2017). In addition, tropisetron protects against amyloid-beta-induced neurotoxicity in vivo by reducing apoptotic and inflammatory markers (Rahimian et al. 2013). Strong evidence confirmed that HG induces apoptosis through the oxidative stress insult and, subsequently activation of the cytokine network (Safhi et al. 2019). Accordingly, TNFα as a major proinflammatory cytokine in DPN can promote the nuclear factor-kappa B (NF-κB) and apoptotic signaling pathways (Evangelista et al. 2018,Urabe et al. 2015). Bax, as a proapoptotic factor, and BCL2, as an antiapoptotic agent, play pivotal roles in the apoptosis process in T1DM (Edlich 2018). Exposure to long-lasting high glucose disturbs pro- and anti-apoptotic balance, which can result in apoptosis insult (Lee et al. 2009,Shi et al. 2018). Activation of pro-apoptotic protein Bax causes the release of cytochrome c from mitochondria that contribute to apoptosis. An elevated ratio of Bax/Bcl-2 may trigger caspase-3 release as a key mediator of apoptosis, and thus plays a critical role in programmed cell death or apoptosis (Busch et al. 2012).

Several reports indicate the anti-apoptotic effect of tropisetron in vivo and in vitro. The neuroprotective effect of tropisetron has been shown in high glucose-induced apoptosis in PC12 cells by reducing the ratio of Bax/Bcl-2 as an in vitro model of diabetic neuropathy (Aminzadeh 2017). Furthermore, the anti-aging effect of tropisetron in the mouse brain was reported by attenuating apoptosis as indicated by Bax and BCL2 changes (Mirshafa et al. 2020). We have recently observed that tropisetron diminished pancreas apoptosis by altering the mitochondrial apoptotic pathway in STZ-induced diabetic rats (Naderi et al. 2020a). Most notably, our findings indicate that diabetes causes a marked increase in Bax and a marked decrease in BCL2 expression in the sciatic nerve tissue, this effect being amenable to reversal by tropisetron. These data may have etiological and therapeutic implications for the management of diabetic neuropathy.

## Conclusion

These findings suggest that tropisetron plays a protective role in sciatic nerve injury induced by diabetes. Moreover, the inflammatory cytokines and apoptosis indices in DPN were inhibited after treatment with tropisetron. This result implied that tropisetron might protect the sciatic nerve by inhibiting the inflammatory response and apoptosis. Thus, we can propose that tropisetron may have healing effects on nerve damage in a neuropathy model induced by STZ. Further studies are essential to detect the probable molecular mechanisms by which tropisetron exerts its protective effects against diabetic neuropathy.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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