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Articulo Original / Original Article

# Evaluation of effect of *Nerium oleander* against STZ induced diabetic neuropathy rat model by reducing NF-ϰB pathway

[Evaluación del efecto de *Nerium oleander* en el modelo de rata con neuropatía diabética inducida por STZ al reducir la vía NF-ϰB]

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**Abstract:** Diabetic neuropathy (DN) is a chronic diabetic complication, which is difficult to manage. The current investigation evaluates the effect of *Nerium oleander* (NO) in the management of diabetic neuropathy (DN). Diabetic neuropathy was induced by streptozotocin (STZ) [60 mg/kg, i.p.] and treated with NO 150 mg/kg and 300 mg/kg, per oral (p.o.) for two week. Blood glucose level, analgesic response, muscle coordination, and intestinal transit were estimated in DN rats. Oxidative stress and inflammation were estimated in DN rats. Loss of muscle coordination, swim Endurance and analgesic response were attenuated by NO treatment in DN rats. Mediators of inflammation and oxidative stress parameters were ameliorated in NO treated DN rats. The given study concluded that NO has beneficial for the management of DN by regulating oxidative stress and inflammatory mediators.

**Keywords:** Diabetic neuropathy; *Nerium oleander*; STZ; Muscle coordination; Intestinal transit.

**Resumen:** La neuropatía diabética (DN) es una complicación diabética crónica, que es difícil de manejar. La presente investigación evalúa el efecto de *Nerium oleander* (NO) en el tratamiento de la neuropatía diabética (DN). La neuropatía diabética fue inducida por estreptozotocina (STZ) [60 mg/kg, ip] y tratada con NO 150 mg/kg y 300 mg/kg, por vía oral (p.o.) durante dos semanas. En ratas DN se estimaron el nivel de glucosa en sangre, la respuesta analgésica, la coordinación muscular y el tránsito intestinal. En ratas (DN) se estimaron el estrés oxidativo y la inflamación. La pérdida de la coordinación muscular, resistencia a la natación y respuesta analgésica se atenuaron con el tratamiento con NO en ratas DN. Los mediadores de la inflamación y los parámetros del estrés oxidativo mejoraron en ratas DN tratadas con NO. El estudio presentado concluyó que el NO tiene beneficios para el tratamiento de la DN al regular el estrés oxidativo y los mediadores inflamatorios.

**Palabras clave:** Neuropatía diabética; *Nerium oleander*; ZTE; Coordinación muscular; Tránsito intestinal

## INTRODUCTION

Diabetes mellitus (DM) is an endocrinal disorder, which affects the metabolism of 2.8% of the world population (Aktas & Gur, 2021; Golden *et al*., 2009). There are several complications associated with diabetes mellitus (DM); diabetic neuropathy (DN) is one of the major complications, which includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system (Medeiros *et al*., 2021). Literature suggests that about 30–50% of all diabetic people are affected by DN (Hicks & Selvin, 2019). Chinese population suffering from type II diabetes shows higher prevalence (60%) rate of DN than global prevalence of it, moreover it is also associated with neuropathic pain (Zhang *et al*., 2020). DN contributes in the enhancement of economic burden, as it result in morbidity by affecting specific areas of nervous system and one of the major cause of amputation (Dyck *et al*., 1993). Management of DN is remain a challenge and there is a need of development of alternative therapy for the treatment of DN.

Diabetic neuropathy associates with the generation of pain and it even affects the nerve associated with other systems of our body, which affects the functioning of cardiovascular and digestive system (Feldman *et al*., 2019). Some of the abnormalities demonstrated in experimental diabetic neuropathy include decreased axonal transport, a reduced nerve conduction velocity, and an increase in resistance to ischemic conduction failure altering nervous signal transduction cascade which is still the facing question (Chung *et al*., 2014). Hyperglycaemia for the long duration time leads to neuronal degeneration due to activation of oxidative and inflammatory pathway, which causes neuropathic pain. Hyperglycaemia stimulates the generation of ROS causes injury to dorsal root ganglion (DRG) and peripheral neurons due to activation of nuclear factor kappa B (NF-κB) in diabetic neuronopathy (Sandireddy *et al*., 2014).

Herbal medicines belongs to family Apocynaceae such as *Gymnema sylvestre*, *Catharanthus roseus*, *Gongronema latifolium* Benth., *Apteranthes europaea* (Guss.) Murb., and *Nerium oleander* has shown promising effect for the management of diabetes and its complications including DN (Bindu & Narendhirakannan, 2019). *Nerium oleander* (NO) is traditionally used as a folk medicine in China. In early times it was assumed that all parts of the NO plant were poisonous to humans, animals and certain insects but now a day's numbers of pharmacological activities are determined. NO is reported to possess several pharmacological activities which are anticonvulsants, antidiabetic, antibacterial, anticancer activity, and antioxidant (Bhuvaneshwari *et al*., 2007; Calderón-Montaño *et al*., 2013; Dey *et al*., 2015; Mohadjerani, 2012; Rout & Kar, 2011). Present report evaluates the protective effect of NO against diabetic neuropathy and also postulates the possible mechanism of its action.

## MATERIALS AND METHODS

### *Procurement and authentication of Nerium oleander*

Leaves of *Nerium oleander* were collected during October to December 2016 from some gardens and local area of Yavatmal district, Maharashtra State, India. The plant was identified by characteristics of prominent mid-rib with thick and glossy leaves and authenticated by S. Karthikeyan and Anand Kumar, Flora of Yavatmal District, Maharashtra and concerned with the Department of Botany, Sant Gadge Baba Amravati University, Amravati (Maharashtra). Voucher specimen was deposited at the institute (voucher specimen sample no. 510255).

### *Preparation of plant extract*

Leaves of *Nerium oleander* were collected from the local vendor, dried under the shed and coarsely powder the dried leaves with grinder. The powdered leaves were kept for maceration in Hydro-alcoholic 1:1 ratio (99.9%) medium for 72Hrs at room temperature and filtered. Percentage yield obtained was 5.022% w/w.

### *Experimental animals*

Sprague Dawley rats (m/f; Age: 8 weeks; 250-300 gm) were housed under standard environmental conditions (22 ± 2°C; humidity 55- 60%, light- dark cycle of 12 hours each) and fed with standard pellet diet and water. The protocol was reviewed and approved by the Institutional Animal Ethical Committee (IAEC) under research project number 650/02/C/CPCSEA/1/2016.

### *Induction of diabetic neuropathy*

All the rats were separated in two different groups such as control group (n=6) with receives vehicle and diabetic group (n=18) with receives STZ (60 mg/kg,

i.p.), rats with > 200 mg/dL blood glucose considered as diabetic. All the diabetic rats were kept for 4 week for the confirmation of DN. Diabetic group rats were further separated into three different groups (n=6); negative control group which was treated with vehicle after the confirmation of DN; NO 150 and 300 mg/kg receives NO 150 and 300 mg/kg p.o. for the duration of 2 weeks.

***Assessment of physiological parameters***

Tail flick model was used to assess the algesia by analgesiometer. Muscle coordination alteration was assessed with rota road and Swimming Endurance Test (SET) Model. Moreover, neuronal functioning to the smooth muscle of GI track by estimating the intestinal transit time. These physiological functions were assessed after 28$^{th}$ day of induction of diabetes and after 2 weeks of drug treatment.

***Assessment of oxidative stress***

Oxidative stress parameters such as LPO and SOD was determined in brain tissue homogenate of DN rat. MDA level was estimated in the brain tissue as per Ohkawa method at 532 nm. GSH content was determined in the hippocampal tissue by estimating the absorbance at 412 nm.

Level of reactive oxygen species (ROS) was assessed by incubating the tissue homogenate with 2′,7′-dichlorofluorescindiacetate dye at 37°C for 15 min. Fluorescence was measured at 488 nm for excitation and 525 nm for emission. Level of ROS was expressed as picomoles per min per mg of protein.

***Assessment of cytokine level***

Brain tissue and blood isolated from each rat was homogenized under phosphate buffer and level of IL-1β, IL-6, NF-kB, and TNF-α was estimated in the tissue homogenate of DN rat using ELISA method.

***Statistical analysis***

Data are expressed as mean ± SD (n=6). One-way analysis of variance (ANOVA) followed by post-hoc Tukey test was used to compare the various groups with GraphPad Prism software version 8.0.2. Two-way repetitive measure ANOVA followed by post-hoc Bonferroni test was used to find the differences in MWM acquisition data. $p<0.05$ was considered statistically significant.

**RESULTS**

***Effect of Nerium oleander on body weight***

Effect of *Nerium oleander* was observed on the body weight of STZ induced diabetic nephropathic rat on 0$^{th}$, 28$^{th}$ and 42$^{nd}$ day of protocol as shown in Figure No. 1. There was significant reduction in the body weight of STZ treated groups than control group of rats on 28$^{th}$ day of protocol. Treatment with NO significantly ($p<0.01$) improves the body weight compared to negative control group of rat on 42$^{nd}$ day of protocol.

***Effect of Nerium oleander on blood glucose***

**Table No. 1**
**Effect of hydroalcoholic extract of *Nerium oleander* on blood glucose level of rat**

| GROUP | On 3$^{rd}$ day glucose level (mg/dL) | On 28$^{th}$ day glucose level (mg/dL) | On 42$^{nd}$ day glucose level (mg/dL) |
|---|---|---|---|
| Control | 112.16 ± 18.96 | 113.56 ± 11.36 | 114.21 ± 3.39 |
| Negative control | 229.15 ± 22.86$^{\#\#}$ | 339.81 ± 23.36$^{\#\#}$ | 392.26 ± 7.34$^{\#\#}$ |
| NO 150 mg/kg | 215.39 ± 39.08$^{\#\#}$ | 331.76 ± 34.60$^{\#\#}$ | 152.35 ± 8.79** |
| NO 300 mg/kg | 248.89 ± 21.22$^{\#\#}$ | 338.83 ± 23.89$^{\#\#}$ | 126.95 ± 6.09** |

**Mean ± SD (n = 6), $^{\#\#}p<0.01$ compared to control group; $^{**}p<0.01$ compared to negative group**

Effect of *Nerium oleander* was estimated on the level of glucose in the serum of STZ induced diabetic neuropathic rat on 3rd, 28th and 42nd day of protocol (Table No. 1). Level of glucose was enhanced significantly ($p$<0.01) in the serum of STZ treated group than control group on 3rd and 28th day of protocol. Moreover, glucose level was enhanced in negative control group than control group of rat on 42nd day of protocol. There was significant reduction ($p$<0.01) in glucose level in the serum of NO treated group than negative control group of rat on 42nd day of protocol.

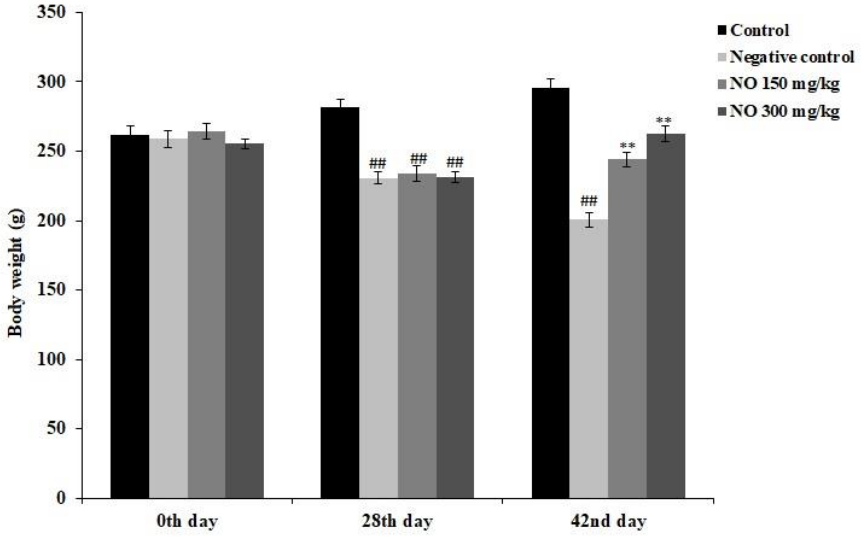


**Figure No. 1**

**Effect of *Nerium oleander* on body weight of STZ induced diabetic neuropathic rats**

Mean ± SD (n=6); ##$p$<0.01 compared to control group; **$p$<0.01 compared to negative control group

***Effect of Nerium oleander on the algesia***

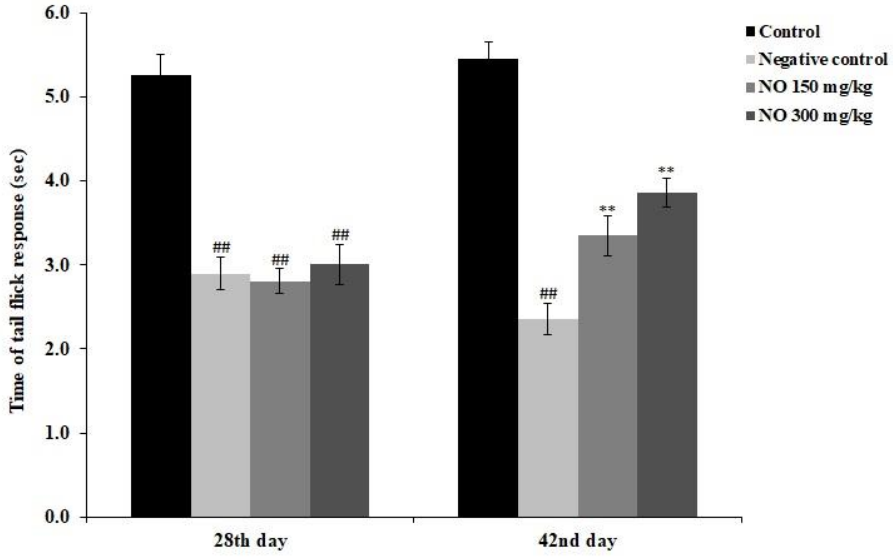


**Figure No. 2**

**Effect of *Nerium oleander* on tail flick response of STZ induced diabetic neuropathic rats on 28th and 42nd day of protocol.** Mean ± SD (n=6); ##$p$<0.01 compared to control group; **$p$<0.01 compared to negative control group

Effect of *Nerium oleander* was observed on neuropathic pain by estimating time of tail flick response of STZ induced diabetic neuropathic rats on 28th and 42nd day of protocol as shown in Figure No. 2. There was reduction in tail flick response of STZ treated group than control group of rat on 28th day of protocol. Tail flick response time was further reduced significantly in negative control group than control group on 42nd day of protocol. Treatment with NO significantly enhances the time of tail flick response in STZ induced DN rat.

***Effect of Nerium oleander on muscle coordination***

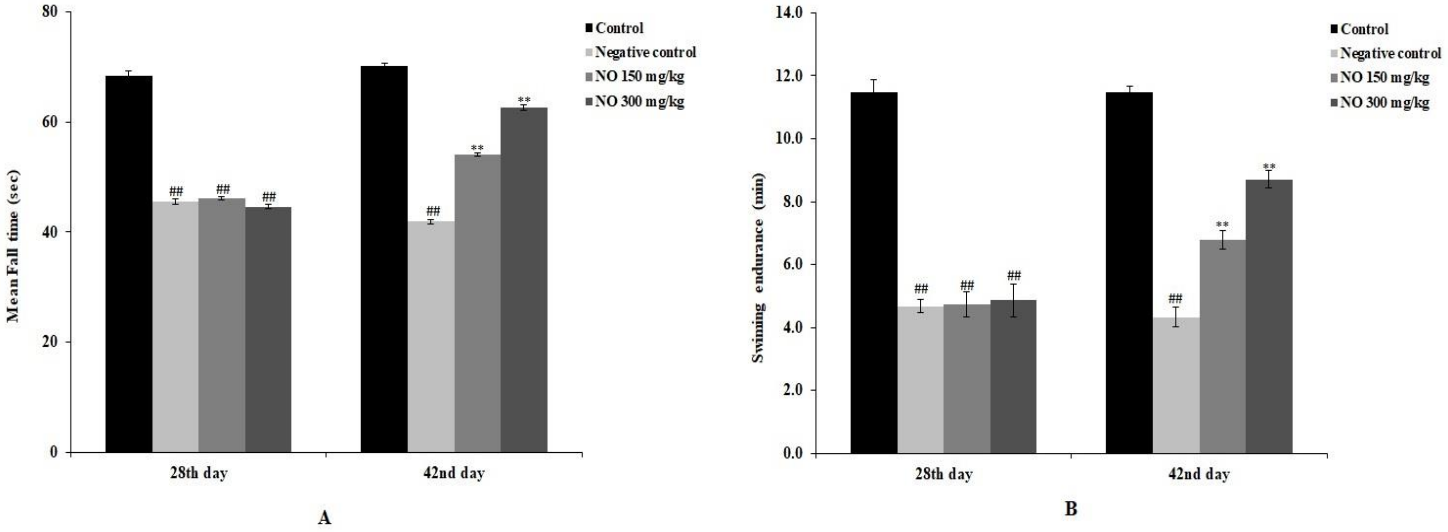


**Figure No. 3**
**Effect of *Nerium oleander* on muscle coordination of STZ induced diabetic neuropathic rats on 28th and 42nd day of protocol. A: Determination of mean fall time on Rota Road apparatus; B: Swimming endurance time on Swimming endurance test.** Mean ± SD (n=6); ##$p$<0.01 compared to control group; **$p$<0.01 compared to negative control group

Muscle coordination was estimated in *Nerium oleander* treated diabetic neuropathic rats on 28th and 42nd day of protocol using rota road apparatus and swimming endurance test as shown in Figure No. 3A & 3B. Mean Fall time was reduced in STZ treated group than negative control group using rota road apparatus on 28th day of protocol. There was significant reduction in fall time of negative control group than control group rat on 42nd day of protocol and treatment with NO improves it (Figure No. 3A). Swimming endurance time was reduced in STZ treated group than negative control group using swimming endurance test on 28th day of protocol. On 42nd day, swimming endurance time was reduced in negative control group than control group of rat and NO reverse it (Figure No. 3B).

***Effect of Nerium oleander on intestinal transit time***

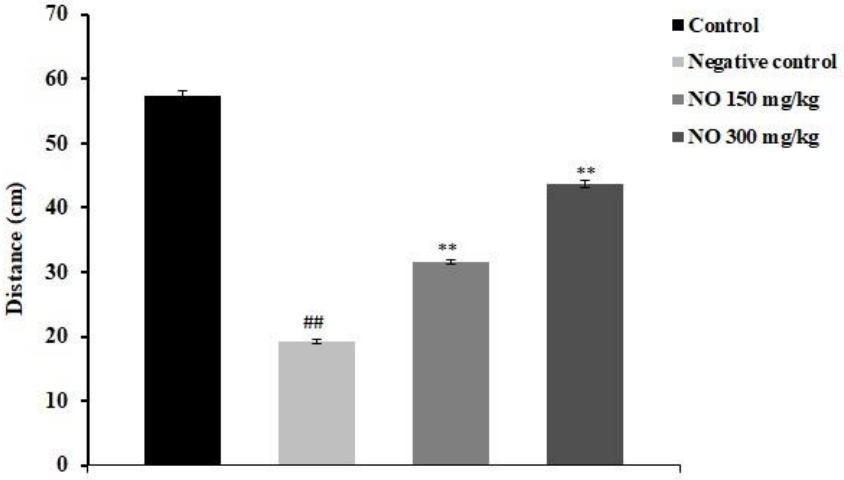


**Figure No. 4**
**Effect of *Nerium oleander* on intestinal transit time of STZ induced diabetic neuropathic rats**
Mean ± SD (n=6); $^{\#\#}p<0.01$ compared to control group; $^{**}p<0.01$ compared to negative control group

Intestinal transit time was estimated by determining the distance travelled by activated charcoal in STZ induced diabetic neuropathic rat as shown in Figure No. 4. There was significant reduction in the distance travelled by activated charcoal in negative control group than control group of rats. Distance travelled by activated charcoal in NO treated group than negative control group of rats.

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***Effect of Nerium oleander on parameters of oxidative stress***

Oxidative stress parameters such as level of reduced glutathione, MDA and ROS in brain tissue of NO treated STZ induced diabetic neuropathic rats as shown in Figure No. 5. There was significant increase in level of MDA and ROS and reduction in reduced glutathione level in brain tissue of negative control group than control group of rats. Treatment with NO ameliorates the altered level of oxidative stress parameters in STZ induced DN rats.

***Effect of Nerium oleander on inflammatory cytokines***

Inflammatory cytokines such as TNF-α, IL-1β, IL-6 and NF-κB was estimated in brain tissue of NO in STZ induced diabetic neuropathic rats. Level of TNF-α, IL-1β, IL-6 and NF-κB was enhanced in brain tissue of negative control group than control group of rats. There was significant reduction in level of inflammatory cytokine in brain tissue of NO treated group than negative control group of rats (Figure No. 6).

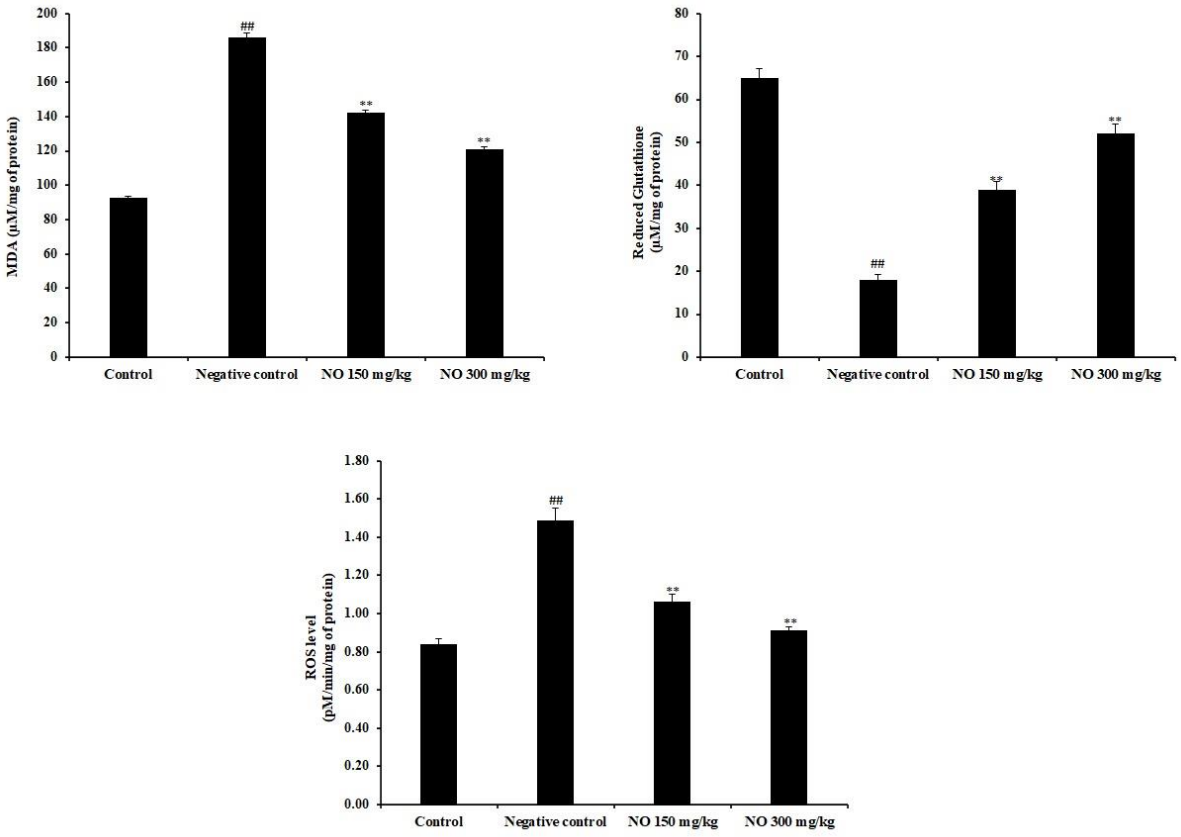


**Figure No. 5**

**Effect of *Nerium oleander* on oxidative stress parameter in brain tissue of STZ induced diabetic neuropathic rats.** Mean ± SD (n=6); $^{\#\#}p<0.01$ compared to control group; $^{**}p<0.01$ compared to negative control group

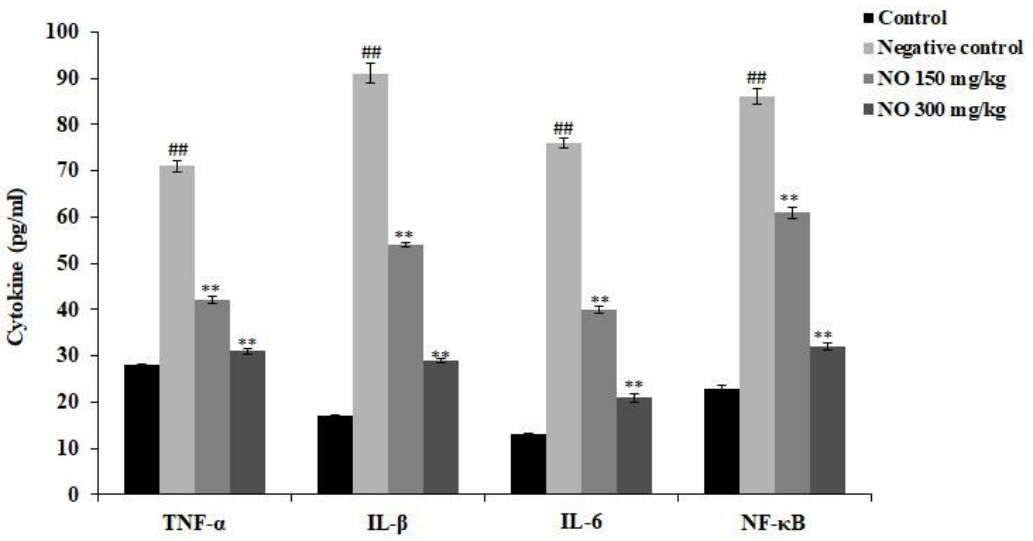


**Figure No. 6**

**Effect of *Nerium oleander* on the level of cytokines in brain tissue of STZ induced diabetic neuropathic rats**

Mean ± SD (n=6); $^{\#\#}p<0.01$ compared to control group; $^{**}p<0.01$ compared to negative control group

## DISCUSSION

Diabetic neuropathy is a chronic complication of diabetes which affects patient suffering from type 1 and type 2 diabetes. DN alters the regulation of neurochemicals, which dysregulate muscle coordination such as skeletal muscle coordination and peristalsis movement and pain sensation (Schreiber *et al*., 2015). Literature reveals that Type I diabetes rapidly leads to rapid development diabetic neuropathy complication (Edwards *et al*., 2008).

STZ was reported to be used to induce type I diabetes in rat model, which was confirm with blood glucose level of 200 mg/dL (Ghasemi & Jeddi, 2023) and data of present report also confirm diabetes induction with similar glucose level. Uncontrolled diabetic condition led to development of diabetic complications including DN. Several studies reveal that DN use to induce in diabetic rat after 4 weeks of induction of diabetes, which confirm with alteration in physiological functions (Sirisha *et al*., 2021) and our report also supports it.

Body weight reduces in diabetes as per clinical evidence, which is one of the major symptoms of diabetes and achievement of effective management of diabetes characterised with improvement in body weight and treatment NO significantly enhances ($p$<0.01) body weight of DN rats.

Hyperglycaemia affects several metabolic pathways which enhances the production of ROS lead to promotion of neuronal apoptosis (Hicks & Selvin, 2019). Regulation of blood glucose level in diabetes prevents development of DN. Physiological parameters like muscle coordination regulated by peripheral nervous system (PNS), DN alters the function neuronal function of PNS causes synaptic plasticity (Muramatsu, 2020). In case of muscle in-coordination occurring due to decreased axonal transport and impaired axon regeneration in the nervous system signal transduction cascade (Shah & Goldberg, 2018). Neuronal dysfunction of PNS also dysregulates intestinal motility, which is commonly associated with DN. Literature suggest that more than 50% of patient suffering from DN has altered gastric motility, commonly known as gastropathy (Krishna *et al*., 2013; Camilleri, 2021). Moreover, sensitivity peripheral tissue enhances, which promotes the function of sensory nerve causes algesia (Kocot-Kępska *et al*., 2021). These all are the physiological behaviours which dysregulated in DN. Regulation of blood glucose in diabetic rats prevents the development of DN symptoms (Feldman *et al*., 2019) and our study suggest that NO treatment reduces the blood glucose level which contribute in the prevention of altered physiological functions and development of DN. A study reveals that treatment with *Selinum vaginatum* root extract improves physiological behaviours like muscle coordination, gastric motility and pain sensation in DN rats (Saraswat *et al*., 2020) and drug used for the management of DN confirm with the improvement of physiological functions. Data of study shows that treatment with NO ameliorates the altered physiological functions like like muscle coordination, gastric motility and pain sensation in DN rats.

There are several pathway including oxidative stress and inflammatory involved in the development of neuropathy in diabetic complications (Fang *et al*., 2022). Hyperglycaemia for the chronic period contributes to alteration of biochemicals, which modulates mitochondrial function and altered the metabolic pathways of several biochemicals lead to reduction in production of endogenous antioxidant molecules in tissue and promotes the overproduction of ROS (Matough *et al*., 2012). ROS generates formation of superoxide anions and free radicals, which are highly active in nature. These free radicals enhance the process of LPO, which impairs the function of cellular membrane by degrading the membrane due to oxidative degradation of polyunsaturated fatty acids (Ayala *et al*., 2014). Metabolic product of polyunsaturated fatty acid is MDA, which reported to be overproduced with the increase in free radicals in patient suffering from DN (Giri *et al*., 2018). Increase level of MDA represents the oxidative stress status in disease individual, which is also found to be enhanced in DN rats of our study. Moreover, GSH is an antioxidant molecule available in reduced and oxidised form, ratio of oxidised to reduced form of GSH increases represents anti stress function and vice versa (Alkazemi *et al*., 2021). Reduced GSH improves the neuronal capacity to metabolize the $H_2O_2$, which is responsible for generation of reactive oxygen species. This oxidative stress and antioxidative stress parameters exist in balance condition in healthy individual, which get disturb in disease condition due to increase production of ROS. Antioxidant drugs has shown promising effect in DN, as it reduces the production of ROS and thereby attenuates the altered level of

GSH and MDA (Ashok *et al*., 2022). Moreover several herbal medicines used for the management of DN, shown promising antioxidant properties to prevent development of diabetic neuropathy in diabetic rats (Saraswat *et al*., 2020). Data of presented report also suggest that treatment with NO ameliorates the altered level of ROS production and level of reduced GSH and MDA in DN rats.

The inflammatory pathway is involved in several chronic disorders including DN, oxidative stress and increase in production of ROS in diabetes promotes the activation of NF-kB (Oguntibeju, 2019). Inflammatory cytokines such as IL-1β, IL-6 and TNF-α majorly involved in diabetic complications, which increase due to activation of NF-kB (Suryavanshi & Kulkarni, 2017). These cytokines stimulate the inflammatory cells such as macrophages, T-cell and monocytes, which promotes inflammatory response and activation of apoptosis pathway leads to DN. Literature reveals that regulation of NF-kB is a effective target for the management of DN (Liu *et al*., 2017) and data of the study suggest that treatment with NO reduces the level of NF-kB and inflammatory cytokine in DN.

## CONCLUSION

In conclusion, study reveals that *Nerium oleander* (NO) regulates blood glucose in diabetes, which improves muscle coordination, analgesia and gastropathy in STZ induced DN rat by regulating NF-kB pathway. NO has shown promising effect against development of DN, as it reduces production of ROS directly on the basis of its antioxidant property and redugulation of glucose also reduce it, which attenuates the inflammatory pathway and reduces neuronal apoptosis too. Data of report supports that treatment with NO could be used clinically for the management of DN.

### *Availability of data and materials*

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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