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Research Article
Neuroprotective Effects of Dapagliflozin Alone and in Combination with Coenzyme Q10 in Streptozotocin-Induced Diabetic Neuropathy

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Abstract

Background and Objective: Diabetic neuropathy is a frequent consequence associated with diabetes, characterized by peripheral nerve damage and chronic pain. Diabetic neuropathy arises due to prolonged hyperglycemia, which results in oxidative stress and impairs neuronal function. The current investigation aims to assess the neuroprotective impact of dapagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor in combination with Coenzyme Q10. **Materials and Methods:** A single dose of Streptozotocin (55 mg/kg/i.p) was administered in the male wistar rats to induced diabetes. The progression of neuropathic pain in diabetic rat was assessed for over four weeks. After four week the rats with neuropathic pain were divided into five groups and the treatment were carried out. Rats with neuropathic pain were treated dapagliflozin (1 mg/kg/p.o.), Coenzyme Q10 (10 mg/kg/p.o.) and dapagliflozin (1mg/kg/p.o.)+Coenzyme Q10 (10 mg/kg/p.o.) combined for 2 weeks (4 week for development of neuropathy and 2 weeks for treatment, so total duration of the study was 6 week). The effectiveness of the test drug treatment was assessed by evaluating behavioral parameters (mechanical and cold allodynia, thermal and mechanical hyperalgesia, motor coordination) and biochemical parameters (blood glucose level, tissue level of lipid peroxidation, reduced glutathione, superoxide dismutase, catalase and nitrite level). Data were analyzed using GraphPad Prism 8.0.1 and expressed as Mean±SEM, $p<0.05$ was considered significant. **Results:** Rats with neuropathic pain showed a significant alteration in both, behavioral as well as biochemical parameters. Treatment with dapagliflozin and CoQ10 significantly improved the altered level of behavioral and biochemical changes. The combined treatment with dapagliflozin and CoQ10 significantly reversed streptozotocin-induced neuropathy more effectively than individual drug treatment. **Conclusions:** Coenzyme Q10 and dapagliflozin have neuroprotective effect both individually and when combined, which may be attributed to their powerful antioxidant capacity and neuroprotective effects.

Key words: Diabetic neuropathy, oxidative stress, biomarkers, antioxidants, hyperglycemia, streptozotocin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetic neuropathy (DN) is a frequent and challenging consequence associated with diabetes. Diabetic peripheral neuropathy (DPN) is characterized by peripheral nerve damage which leads to pain, numbness and sensory deficits, significantly reduced quality of life[1]. DN originates predominantly from persistent hyperglycemia that interfere with carbohydrate protein and lipid metabolism as a result of insufficient insulin. Long-term elevated blood glucose stimulates various metabolic pathways, like the aldose reductase pathway, generation of glycation-derived compound[2], elevated hexosamine pathway flux[3], initiation protein kinase C (PKC) pathway[4] and MAPK activation and inflammatory damage[5]. These pathways all result in the generation associated with ROS, contributing to oxidative imbalance and resultant neuron injury[6]. Oxidative stress acts as a crucial function in development of DN, closely linked to several neuronal dysfunctions, including reduced neuronal support, disrupted axonal growth and damage to DNA. Studies indicate that neuropathy leads to alteration in the level of endogenous antioxidants such as nitric oxide (NO), lipid peroxide, glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) which are responsible for the generation of oxidative stress[7]. This highlights that focusing on oxidative stress might be a promising strategy for treating diabetic neuropathy.

Dapagliflozin (Forxiga®) is a powerful, reversible and selective SGLT2 inhibitor[8]. It becomes an increasingly potential treatment option for managing type 2 diabetes, helping to reduces hyperglycemia and protect neurons from damage caused by oxidative stress[9]. It manifests a variety of advantageous properties including neuroprotective, anti-inflammatory[10], cardiovascular benefit[11], immunomodulation[12] while also mitigating oxidative stress[13]. Coenzyme Q10 also known as ubiquinone, is a fat-soluble compound localized in the mitochondria of nearly all eukaryotes[14]. A CoQ10 is most important for mitochondrial oxidative phosphorylation due to its antioxidant properties. As a powerful antioxidant, CoQ10 safeguards cells against oxidative stress, scavenges free radicals thereby minimizing cellular damage[15]. The rational for combining dapagliflozin and Coenzyme Q10 in treatment of diabetic neuropathy is due to their complementary mechanisms, targeting multiple pathways involved in DN pathogenesis. The combined effects of dapagliflozin and CoQ10 are to enhance neuroprotection, improve neuropathic symptoms, reduce oxidative stress and potentially modify disease progression. Lack of evidences are there about the combined effects of dapagliflozin and CoQ10 on diabetic neuropathy. This research intends to analyze the effect of dapagliflozin and CoQ10, both individually and their combination on peripheral neuropathy in diabetes rat's models.

MATERIALS AND METHODS

Study area and duration: The study was carried out at Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Chandwad, India from December 2024 to May 2025.

Drug and chemicals: Dapagliflozin was procured from Dhamtec Pharma and consultants, Navi Mumbai. CoQ10 and STZ was obtained from Otto Biochemika Pvt. Ltd., Mumbai. All the chemicals and reagents utilized were of high quality.

Experimental animals: Healthy and grown wistar male rats, weighing 180-250 gm were utilized for this study. Animals used in this study were obtained by Laxmi Biotech, Pune. The rats were kept according to a standardized housing protocols which included an environmental temperature range at 23±2°C with a relative humidity of 55±10% and equal duration light and dark cycle. Each rat was kept in individual polypropylene cages bedded with paddy husk. The environment was sustained by according to the guidelines set by the CCSEA. The animals were allowed ad libitum consumption of water, also conventional lab feed provided by VRK Nutritional Solutions, Pune. The investigative methods and procedures utilized within the present study was approval from the IAEC of SSDJ College of Pharmacy, Neminagar, Chandwad (SSDJ/IAEC/24-25/03), ensuring adherence to established guidelines for animal welfare.

Induction of neuropathic pain and experimental design: Animals injected once intraperitoneally with streptozotocin (55 mg/kg), prepared in citrate buffer (0.05 M, pH 4.5)[16]. Glucose levels assessed after 72 hrs. using a glucometer (Dr. Morepen, India). Rats whose glycemic levels exceeded (>250 mg/dL) were chosen for further experimentation. The hyperglycemic rats were observed and assessed using von Frey hair test over a period of 4 weeks for the development of neuropathic pain. Rats with neuropathic pain were separated and further divided into five groups with 6 rats in each group. The treatment was continued for two weeks (4 week for NP and 2 week treatment total study duration was 6 week). The grouping of animals are as follows.

Group I, rats served as control and received citrate buffer 0.5 mL/kg; group II, rats received STZ (55 mg/kg, i.p.) and served as diseases group (Diabetic neuropathy); group III, Diabetic neuropathy rats received dapagliflozin at a dose of 1 mg/kg, p.o. for two week[17], group IV, Diabetic neuropathy rats received coenzyme Q10 at a dose of 10 mg/kg, p.o. two week[18] and group V, Diabetic neuropathy rats received the combination of dapagliflozin (1 mg/kg, p.o.) and coenzyme Q10 (10 mg/kg, p.o.) two week. At the end of treatment period various parameters were assessed to determine the effects of dapagliflozin and coenzyme Q10.

Evaluation of general parameters and blood glucose level: Change in the body weight, amount of feed and water consumption were monitored every week and at the end of treatment period. The rats were anesthetized using sodium pentobarbital (40 mg/kg/i.p.) as an anesthesia. Blood was withdrawn by retro orbital plexus technique and the blood glucose level was assessed using digital glucometer.

Evaluation of behavioral alterations: The behavioral parameters were evaluated at the end of treatment period and the output was recorded. The Von Frey hair filament was used to assess a mechanical allodynia which increased pressure exerted on the paw using a filament until it bent and recorded the reaction as a 50% gm threshold[19,20]. Cold allodynia was assessed through the application of an acetone drop, recording the numbers of shaking or licking by hind paw[21]. Thermal hyperalgesia evaluated utilizing Eddy's hot plate method, measuring the duration taken for the paw to lick or jump at temperature 55±0.5°C measured[22]. Randall-Selitto apparatus assessed utilizing mechanical hyperalgesia measured through exerting pressure on the paw until a withdrawal movement noted and this was indicated as % compression break (% CBK)[23]. The Rota Rod test was used to assess motor coordination. In this test, individual rats were placed on a rotating drum set at 20 rpm for 1 min[24]. The number of rats that falling from drum during that minute was recorded[25].

Assessment of the markers of oxidative stress

Tissue homogenization: At the final stage of the experiment the rats were sacrificed using cervical dislocation. The sciatic nerves have been carefully removed and rinsed with ice-cold Tris-HCl buffered saline. Sciatic nerves were carefully slice thin pieces, stored in a cold 0.25M sucrose solution rapidly absorbed onto filter papers. Next to preparation, using cold Tris HCL buffer sciatic nerve were mincing and processed into 10% w/v homogenate. The homogenate underwent centrifugation, resulting clear supernatant collected for measuring changes in markers of oxidative stress[26].

Estimation of MDA, NO, SOD, GSH and CAT: Malondialdehyde (MDA) concentrations were quantifying to assess lipid peroxidation (LPO). The tissue supernatant combined with TBA and TCA reagent. The solution after heating shows pink colour. The absorbance of the colour change was determined at a wavelength of 532 nanometers using a spectrophotometer. Standard solutions of MDA were employed to calibrate the assay[27]. The Griess reagent assay was estimated by measuring tissue nitrite levels. Homogenized samples are mix with the Griess reagent, incubate absorbance was measuring spectrophotometrically measurements were taken at 540 nm and compared to a standards curve prepared with reagent of sodium nitrite[28].

The level of superoxide dismutase (SOD) quantified through determining the ability to inhibit conversion of hydroxylamine into the nitrite. Reduction detected at 480 nm noted the level of SOD was expressed in units per milliliter of tissue[29]. The level of reduced glutathione (GSH) assessed through reacting with DTNB, which produced a yellow product that was considered at 412 nm. GSH levels were quantified utilizing a standard curve created from standard solutions of glutathione[30]. Catalase (CAT) was assessed through monitoring the breakdown of hydrogen peroxide into water and oxygen, resulting in the formation of a yellow-colored complex. The level of CAT represented by micromoles of hydrogen peroxide utilized per minute per milligram of protein[31].

Statistical analysis: The GraphPad Prism (Version 8.0.1) was utilized in analyze the data. Result are presented as Mean±SEM. A t-test was conducted to examine differences between the two groups. Dunnett's multiple comparisons test was conducted after performing one-way ANOVA with $p<0.05$ were consider significantly. In comparisons between DN group relative to control rats statistically significant #$p<0.05$, ##$p<0.01$, ###$p<0.001$ and significance levels to comparison of treated and DN rats *$p<0.05$, **$p<0.01$, ***$p<0.001$.

RESULTS

Effects of Dapagliflozin, CoQ10 and their combination on body weight, feed and water intake: A significantly reduction in body weight ($p<0.001$) noted within DN animals relative

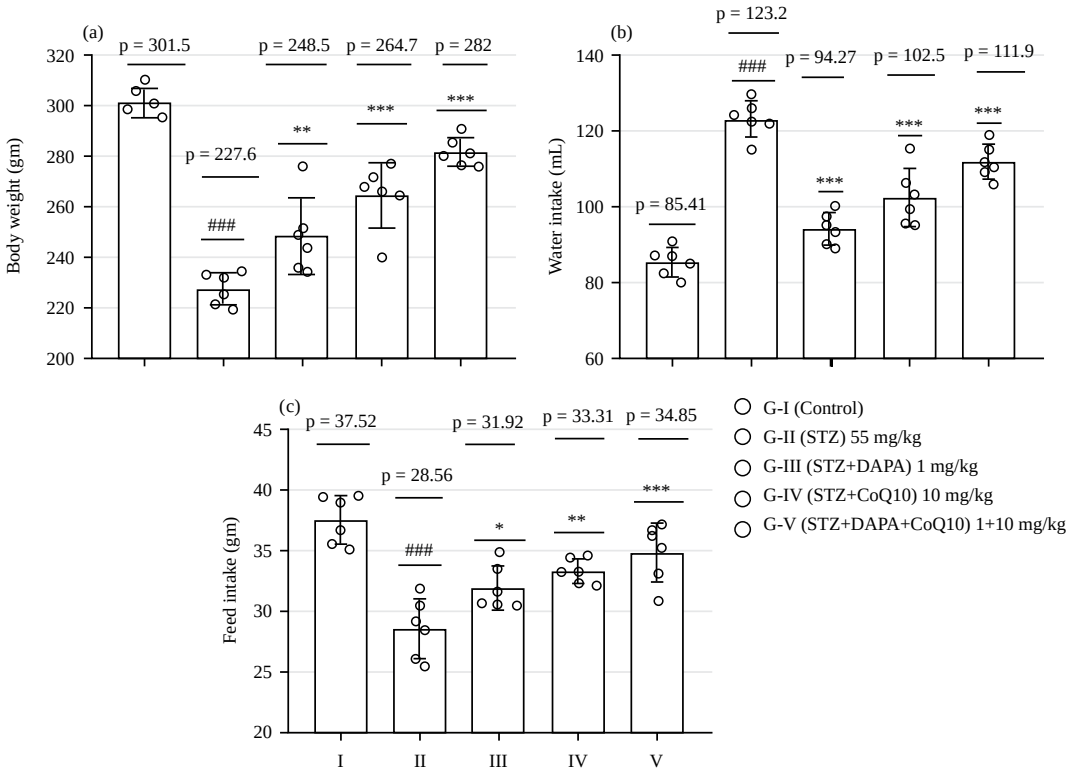


Fig. 1(a-c): Effect of dapagliflozin, CoQ10 and their combination on (a) Body weight (b) Water intake and (c) Feed intake

Data are presented as Mean±SEM (n = 6). Analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

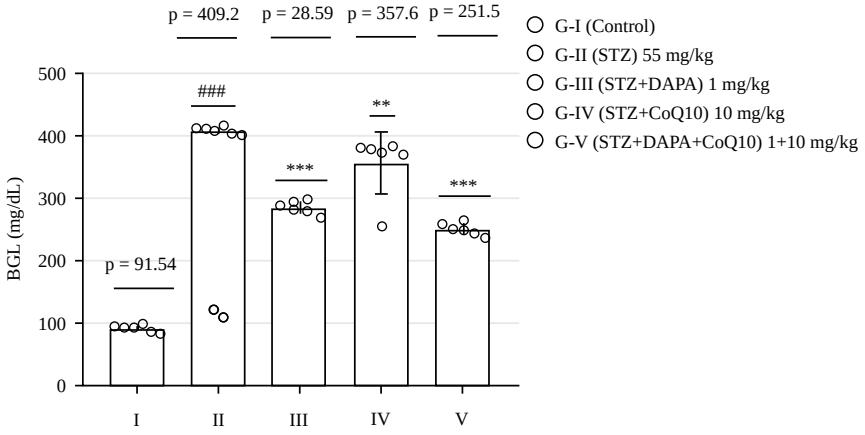


Fig. 2: Effect of dapagliflozin, CoQ10 and their combination on BGL (6th week) in STZ induced DN rats

Data are presented as Mean±SEM (n = 6), Analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to the control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

to control group. While DN animals treated dapagliflozin, Coenzyme Q10 along with combined therapy showed significant rise in body weight relative to DN animals. Whereas, water intake exhibited a significant raised comparison with controls (p<0.001). However, treatment with dapagliflozin, CoQ10 and in combination led to a significantly (p<0.001) decreased water intake relative with DN animals. Furthermore, feed intake similarly significant (p<0.001) improved in treated groups relative to DN rats (Fig. 1a-c).

Effect of Dapagliflozin and CoQ10 on blood glucose level (BGL): BGL was assessed 72 hrs after STZ injection. DN animals showed substantially higher (p<0.001) glucose level relative

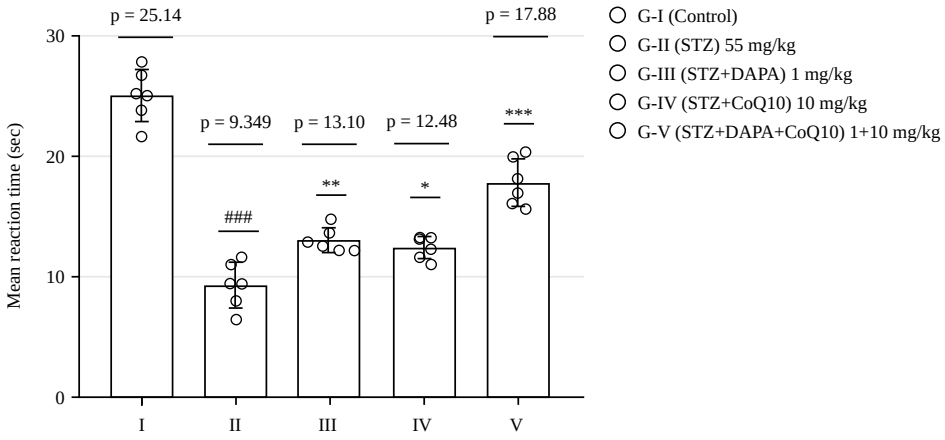


Fig. 3: Effect of Dapagliflozin, CoQ10 and their combination on thermal hyperalgesia

Data are presented as Mean±SEM (n = 6), Analysis was performed by applying ANOVA followed by Dunnett 't' test. ### p<0.001 comparison to control and *p<0.05, ** p<0.01, ***p<0.001 comparison to DN group

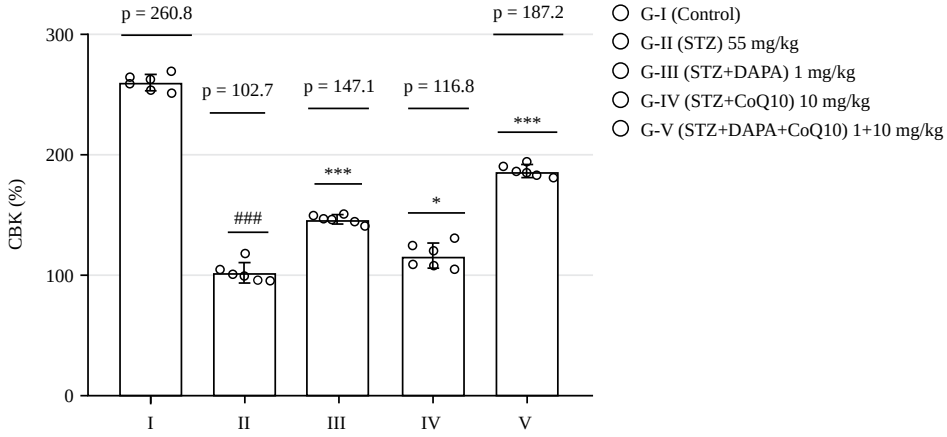


Fig. 4: Effect of dapagliflozin, CoQ10 and their combination on mechanical hyperalgesia

Data are presented as Mean±SEM (n = 6), Analysis was performed by applying ANOVA followed by Dunnett 't' test. ### p<0.001 comparison to the control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

with control rats. This elevated BGL persisted in diabetic rats until the end of 4th week. Notably, DN rats receiving dapagliflozin exhibited greater significant (p<0.001) decline among BGL, CoQ10 alone showed significant decrease in BGL (p<0.01). Moreover, combined therapy of dapagliflozin, CoQ10 led to a significant more pronounced lowering in BGL (p <0.001) relative toward untreated DN animals (Fig. 2).

Effect of dapagliflozin, CoQ10 and their combination on behavioral parameters

Effect of dapagliflozin, CoQ10 on thermal hyperalgesia using Eddy's hot plate: Thermal response became examined utilizing Eddy's hot plate and represent mean reaction time in seconds. Reaction time in DN animals demonstrated a significant lower (p<0.001) relative with control group. Administration of dapagliflozin show significantly increases (p<0.01), CoQ10 alone shows significant elevation (p<0.05). Notably, combined therapy yielded a more pronounced increase in compared with the reaction time of DN group (p<0.001) (Fig. 3).

Effect of dapagliflozin and CoQ10 on mechanical hyperalgesia using Randall Selitto Analgesiometer: The Randall-Selitto Analgesiometer was employed to evaluate mechanical hyperalgesia. A total of six male rats were utilized and indicated as % CBK. DN animals exhibited substantial decrease of % CBK (p<0.001) relative into control rats. Dapagliflozin administered alone yielded a significantly (p<0.001) enhancement in % CBK, DN animals received CoQ10 treatment show significantly (p<0.05) raised in % CBK relative to DN animals and combination therapy yielding a more pronounced higher effect (p<0.001) (Fig. 4).

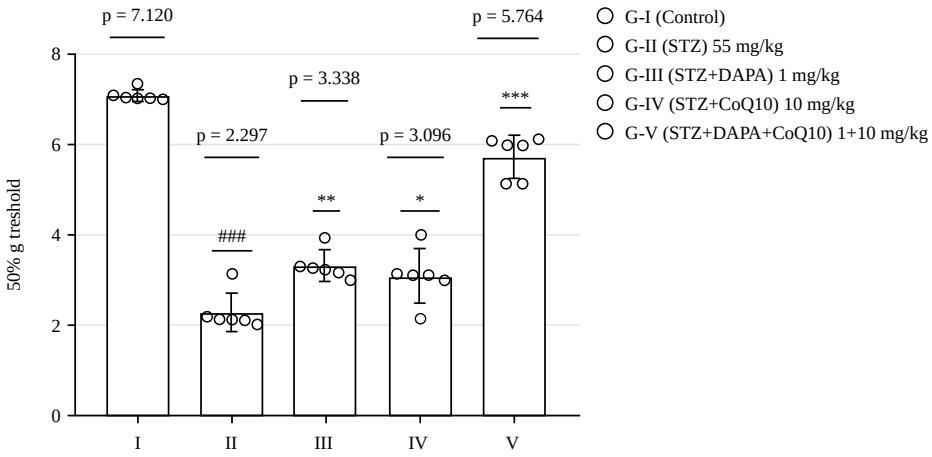


Fig. 5: Effect of dapagliflozin, CoQ10 alone and in combination on mechanical allodynia using Von Frey filament test

Data are presented as Mean±SEM (n = 6). Analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to the control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

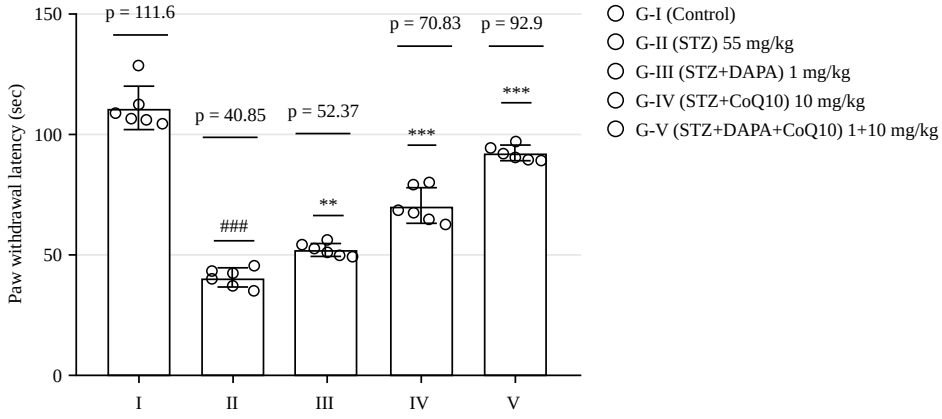


Fig. 6: Effect of dapagliflozin, CoQ10 alone and in combination on cold allodynia with acetone

Data are presented as Mean±SEM (n = 6). Analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to the control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

Effect of dapagliflozin and CoQ10 on mechanical allodynia using von frey filaments: Von frey filament testing was used to assess mechanical allodynia and were represented by 50 % gm threshold. DN animals displayed significantly lower 50 % gm threshold ($p<0.001$) relative with control group. DN animals received a dapagliflozin alone demonstrated a significantly ($p<0.01$) raised, CoQ10 ($p<0.05$) increases with in 50 % gm threshold shows significant result as compared to DN rats. Notably, combination therapy yielded a ($p<0.001$) more pronounced elevation in 50 % gm threshold relative with DN animals. (Fig. 5).

Effect of dapagliflozin and CoQ10 on Cold allodynia using Acetone: Paw Withdrawal response time was significant lower in DN animals ($p<0.001$) relative with control group. Administration of dapagliflozin significantly increase paw withdrawal time ($p<0.01$), Notably administration of CoQ10 alone and concurrent treatment with dapagliflozin and CoQ10 displayed highly pronounced statistical significance elevation ($p<0.001$) (Fig. 6).

Effect of dapagliflozin and CoQ10 on Rota rod test for evaluating motor coordination: The difference in time to fall from the rotating rod was used as index of muscle relaxation. Muscle relaxation exhibits a substantial decrease ($p<0.001$) among DN rats relative with control group. Dapagliflozin alone treatment showed a significant increase ($p<0.05$), CoQ10 alone exhibited significant raised ($p<0.01$) fall of time. Whereas index of muscle relaxation displayed a more significant ($p<0.001$) elevation as a combination treatment with dapagliflozin and CoQ10 (Fig. 7).

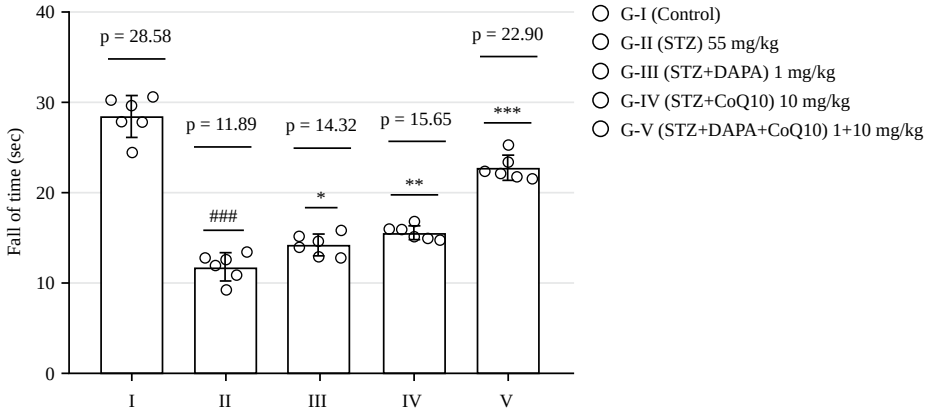


Fig. 7: Effect of dapagliflozin, CoQ10 and their combination on using rota rod test for muscle grip strength

Data are presented as Mean±SEM (n = 6). Analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

Effect of dapagliflozin, CoQ10 alone and in combination on oxidative stress biomarkers

Lipid Peroxidation (LPO): In diabetic neuropathy rats, levels of lipid peroxides within the sciatic nerve homogenates were substantially higher (p<0.001) compare with control group. Dapagliflozin, CoQ10 alone and combination therapy treatment displayed a more significant decrease in LPO levels after a 14 days treatment period (p<0.001) (Fig. 8a).

Nitric oxide (NO) levels: A substantial rise (p<0.001) in NO levels was noted within DN animals. Administration of dapagliflozin led to a substantial declined (p<0.01) within NO levels, whereas coenzyme Q10 alone exhibited a lower significantly decrease (p<0.05) NO levels. Notably, combination therapy with dapagliflozin and CoQ10 resulted in an even more pronounced reduction (p<0.001) in nitric oxide levels compare with DN groups (Fig. 8b).

Superoxide dismutase (SOD) activity: Diabetic neuropathy group displayed a notable (p<0.001) reduction concerning SOD activity. However, treatment with dapagliflozin (p<0.05) and Coenzyme Q10 (p<0.01) pronouncedly improved SOD activity. Furthermore, combination therapy with dapagliflozin and CoQ10 produced a notably increase in SOD activity (p<0.001) in comparison with the DN rats (Fig. 8c).

Reduced glutathione (GSH) levels: A pronounced decline (p<0.001) glutathione level was noted within DN rats. While administration of dapagliflozin (p<0.001), CoQ10 (p<0.01) alone showed substantial increase GSH level along with combined of both substantially improved glutathione activity (p<0.001) (Fig. 8d).

Catalase (CAT) Activity: Catalase activity was substantially decrease (p<0.001) within DN group. Administration of dapagliflozin (p<0.01), Coenzyme Q10 alone (p<0.05) showing a significant elevation along with combined shows more substantially increase catalase levels (p<0.001) (Fig. 8e).

DISCUSSION

Diabetes mellitus represents a metabolic condition attributed to inadequate insulin secretion, impaired insulin action or both combinations, leading to increased hyperglycemia[32]. Prolonged inadequately controlled hyperglycemia in diabetic patients can lead to a range of vascular complications, impacting both small (microvascular) and large (macrovascular) vessels[33]. DM plays a crucial role in gluconeogenesis[34]. Chronic hyperglycemia is recognized as a primary contributor to complications related to DM, such as diabetic neuropathy. Research has shown elevated blood glucose levels play a critical onset of oxidative stress[18]. DN occurs as a result of poorly managed hyperglycemia. Common symptoms of diabetic neuropathy include pain, delayed nerve conduction and tingling sensations within limbs[35].

In this research, one-time administration of streptozotocin was used to produce diabetes in rats to model DN. Use of streptozotocin as antibiotic that selectively destroys pancreatic islet β-cells, is a commonly used approach for developing experimental models of T1DM. The reliability, validity of STZ induced DN rodent model have been extensively demonstrated in previous research[36]. STZ-induced insulin deficiency and elevated blood glucose levels have been widely studied characterized by rodent models[37]. A DN major complication of diabetes mellitus, marked in manifesting as neuropathic symptoms in individuals after

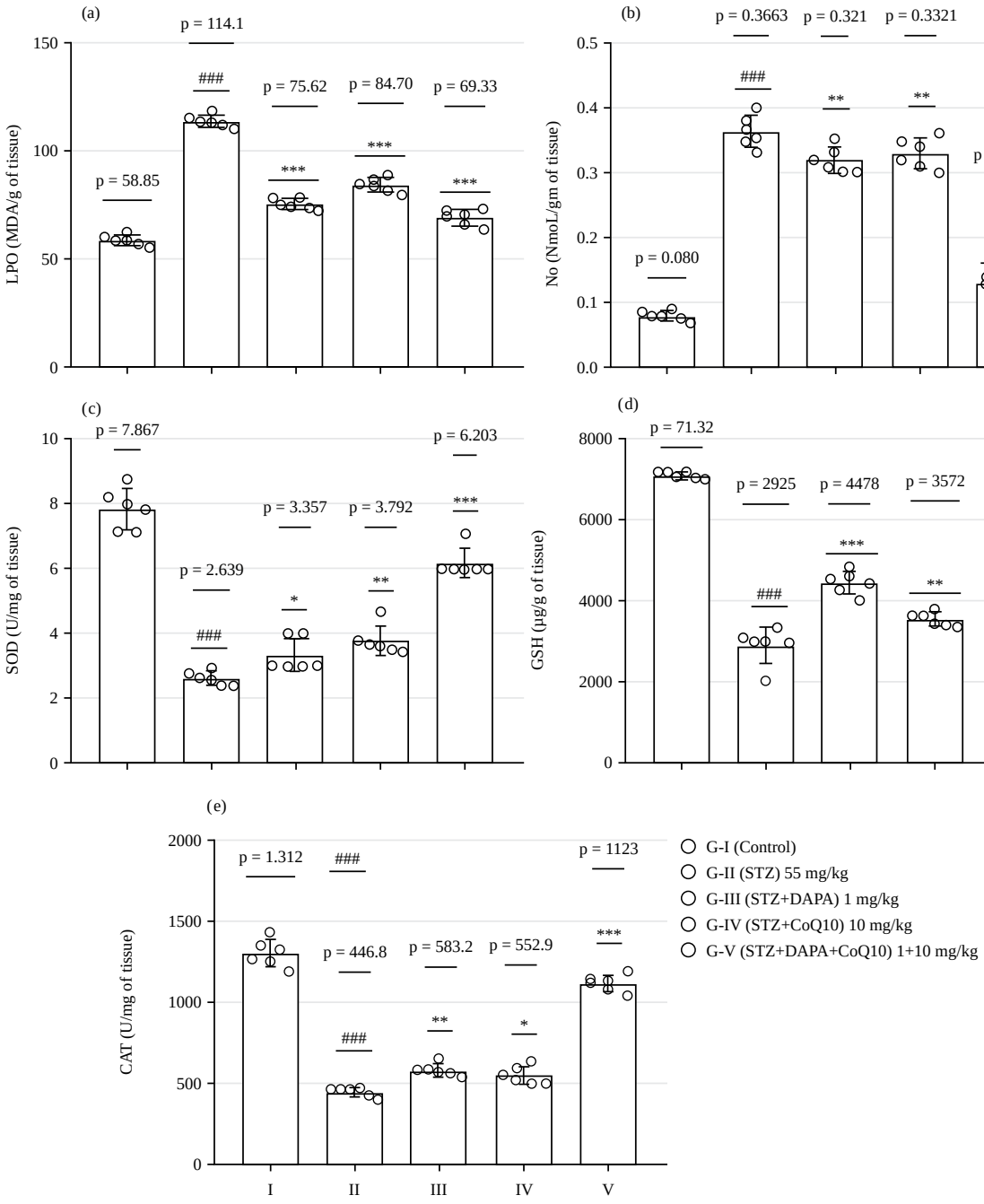


Fig. 8(a-e): Effect of dapagliflozin, CoQ10 and their combination on Lipid Peroxidation level, (b) Effect of dapagliflozin, CoQ10 and their combination on Nitric Oxide level, (c) Effect of dapagliflozin, CoQ10 and their combination on Superoxide Dismutase level, (d) Effect of dapagliflozin, CoQ10 and their combination on Reduced Glutathione level and (e) Effect of dapagliflozin, CoQ10 and their combination on Catalase level

Data are presented as Mean±SEM (n = 6), analysis was performed by applying ANOVA followed by Dunnett 't' test. ###p<0.001 comparison to control and *p<0.05, **p<0.01, ***p<0.001 comparison to DN group

excluding causes that may lead to neuropathy. Managing DN involves controlling hyperglycemia and tackling cardiovascular risk factors. Furthermore, STZ has been shown to activate protein kinase-C, which results in the formation of ROS, ultimately leading to nerve injury[38]. The present study primarily focuses on antioxidant therapy as a potential intervention. Antioxidants are bioactive compounds that decrease oxidative stress (OS) by scavenging free radicals,

thereby exhibiting potential in reducing autoimmune diseases, by inhibiting the process of generating free radicals and safeguarding cells against oxidative harm. Our study showed that administering dapagliflozin, CoQ10 and their combination resulted in notable decreases in hyperglycemia observed in rats. These results align with earlier research[18].

This investigation utilized behavioral indicators to assess nociceptor functioning in the behavioral assessments in DN rats included the Von frey test, Randall-Selitto apparatus, Hot plate method, Rota-Rod test and Cold allodynia using acetone. Treatment with dapagliflozin and CoQ10 significantly improved these parameters, indicating enhanced protection against painful stimuli, particularly when used together. However, treated with dapagliflozin, Coenzyme Q10 significantly reduced these lipid levels. Notably, the combined treatment produced an even stronger effect, highlighting a synergistic benefit.

The oxidative stress generated by a disproportionate proportion between reactive species and antioxidants are pivotal contributor to the pathophysiology of diabetes[39,40]. In this research demonstrate that the treatment with dapagliflozin and CoQ10 both individually and in combination significantly reduce lipid peroxidation (LPO) the levels in rats were compared to DN. Furthermore, antioxidant enzyme activities including CAT, SOD, GSH, were substantially elevated within treatment groups, indicating a mitigating action against oxidative stress. Notably, DN rats exhibited elevated concentrations of nitric oxide, besides showed a significant decline after administration of dapagliflozin and CoQ10 especially in administered together.

This study examined the protective benefits of dapagliflozin in a diabetes model induced by streptozotocin. Recent studies have confirmed that dapagliflozin effectively combats oxidative stress associated with diabetes conditions, leading further support to our observations of its neuroprotective properties. Dapagliflozin a SGLT2 inhibitor, has been results showed that dapagliflozin mitigated oxidative stress development, enhance nerve conduction velocity and supporting it's nephroprotective effect. This protective effect was mediated through anti-apoptotic mechanisms[41]. Evidence from another reported study suggests that the combination of CoQ10 and N-acetylcysteine has a synergistic antioxidant effect[18]. CoQ10 has been identified potent antioxidant that helps to provide defense against multiple diseases, including diabetes and its related cardiovascular issues[15]. Recent studies suggest that CoQ10 works through several mechanisms, such as lowering oxidative stress, providing anti-inflammatory benefits and managing glucose and lipid metabolism. Additionally, CoQ10 has shown to alleviate diabetes-induced oxidative damage, boost the production of free radical-scavenging enzymes and nerve regeneration[42]. Recent study highlights the CoQ10 has been found to mitigate neuronal injury in consistent with our findings of ameliorated nerve function[7].

Our results demonstrate that the combination therapy significantly reduced oxidative stress markers, improved lipid profiles, enhanced mitochondrial function and exerted neuroprotective effects, ultimately leading to improved action potential conduction in the sciatic nerve fibers of STZ animals. Research highlighted dapagliflozin and CoQ10 combination therapy suggesting an innovative strategy for DN treatment and management.

CONCLUSION

This investigation focused on neuroprotective impact of dapagliflozin, CoQ10 in rodent model suffering from streptozotocin induced neuropathic pain, along with main goal of assessing their effectiveness in relieving neurological symptoms and exploring the underlying mode of action involved. The combination therapy dapagliflozin and CoQ10 led to a notable decrease in neuropathic pain condition and associated with enhanced behavioral, biochemical outcomes along with increased antioxidant levels relative to the control groups. These combination treatment significantly alleviated hyperalgesia and allodynia and more effectively suppressed oxidative stress progression in diabetic neuropathy rats compared to individual treatment. The synergistic interaction between dapagliflozin sodium-glucose cotransporter 2 inhibitory action and CoQ10 antioxidant properties played a crucial role in mitigating oxidative stress, inflammation and mitochondrial dysfunction. These mechanisms contributed to the alleviation of neuropathic pain and the improvement of nerve function.

These findings suggest that this combination of dapagliflozin and coenzyme Q10 may offer a novel and effective treatment managing neuropathic pain, improving quality of life and reducing the risk of complications associated with diabetic neuropathy. This combination acts as a powerful antioxidant, helping to safeguard against the changes associated with DN. Further research in clinical trials is necessary to evaluate the long-term effectiveness of these combinations in advancing phytochemical-based treatment strategies for managing complications of diabetes.

SIGNIFICANCE STATEMENT

This study demonstrates that dapagliflozin and Coenzyme Q10, particularly when used in combination, can effectively attenuate diabetes-induced neuropathic pain and associated oxidative stress. The findings suggest that combined therapy may provide enhanced neuroprotective benefits compared with either treatment alone, supporting its potential as a therapeutic strategy for managing diabetic neuropathy.

ETHICAL APPROVAL

The experimental procedures and protocols have been reviewed and approved by the Institutional Animal Ethics Committee (IAEC) at SSDJ College of Pharmacy in Neminagar, Chandwad (SSDJ/IAEC/24-25/03).

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