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Research Article
Neuroprotective Effects of Virgin Coconut Oil Solubilized Curcumin in Diabetic Peripheral Neuropathy

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Abstract

Background and Objective: Neuropathic pain or peripheral neuropathy is one of the important secondary complications of diabetes. Preventing the severity of pain is one of the challenges and treatment with supporting therapy may extend the complications as well as the pain threshold. Based on the above objective the present study was designed to evaluate the effect of virgin coconut oil solubilized curcumin (VCOSC) on streptozotocin-induced diabetic neuropathy in rats. **Materials and Methods:** Male albino rats (200-250 g) were used in the entire study. Diabetic peripheral neuropathy (DPN) was induced by the administration of streptozotocin (60 mg/kg, i.p.). The DPN was assessed by evaluating behavioural parameters including mechanical allodynia using Von Frey hair test, cold allodynia using acetone, heat or thermal allodynia using a hot plate, mechanical hyperalgesia using Randall Selitto test and biochemical parameters embracing blood glucose level, endogenous antioxidants such as reduced glutathione, lipid peroxidase, superoxide dismutase and catalase. After 4 weeks of development of DPN, the treatment was started with VCOSC at two different doses (0.66 mg/4 mL/kg) and (1.32 mg/8 mL/kg). **Results:** VCOSC significantly reduced the serum glucose level and considerably increased body weight in treated animals as compared to disease (DPN) animals. The treatment also showed a remarkable change in the paw withdrawal latency in all the methods of evaluation as compared to diseased rats. A high dose of VCOSC was proved to be more effective in the assessment of paw withdrawal latency in mechanical allodynia, cold allodynia, thermal allodynia and mechanical hyperalgesia. The levels of endogenous antioxidants such as reduced glutathione, catalase, superoxide dismutase and lipid peroxidation were significantly improved as compared to diseased rats. **Conclusion:** Streptozotocin (STZ) induced rats shows DPN by altering various behavioural and biochemical parameters. The beneficial protective effects of both the compounds might be due to the strong antioxidant activity.

Key words: Virgin coconut oil, curcumin, streptozotocin, peripheral diabetic neuropathy, hyperglycemia, oxidative stress, antioxidants

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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

Diabetes mellitus is characterized by elevated glucose levels in the blood and it leads to microvascular as well as macrovascular complications[1]. DM is associated with long-term damage, dysfunction and eventual organ failure including the eyes, kidneys, heart, nerves and blood vessels.

Peripheral one of the common secondary complications of diabetes mellitus is peripheral neuropathy[2]. Diabetic peripheral neuropathy commonly occurs in people all over the world and its prevalence increases with the period. The pain associated with DPN is distinguished by tingling, burning, sharpshooting, lancinating, or even an electric shock sensation[3]. Various mechanisms are involved in the genesis of neuropathic pain in diabetic conditions, one of the contributing mechanisms is oxidative stress[4-6]. Streptozotocin (STZ) is reported to damage the pancreas in rats and thereby produces prolonged hyperglycemia[7]. Hyperglycemia produces tissue damage via different mechanisms. One such mechanism includes the generation of oxidative stress and production of free radical[8].

Virgin coconut oil (VCO) is a colourless substance with a fresh coconut scent that has been widely used in cooking, baking, confectionery, infant meals and cosmetics. It is also used in cosmetics to improve and nourish skin, as well as to enhance beauty and stimulate hair growth[8]. It was reported to take care of oxidative stress in various conditions by increasing the antioxidant defence system, cleaning up free radicals and lowering lipid peroxidation[9]. Curcumin (CUR) is a yellow polyphenolic pigment obtained from *Curcuma longa* Linn, also known as Turmeric and is a member of the Zingiberaceae family. CUR is well known for its anti-inflammatory, hepato-protective, anti-diabetic, anti-cancer and antioxidant activity. VCOSC is reported to show good protective activity against skin papilloma in mice[10]. The present study was designed to establish the scientific basis and demonstrated the neuroprotective effect of the combination of two antioxidants i.e., virgin coconut oil solubilized curcumin (VCOSC) in streptozotocin-induced diabetes rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Pharmacology, SNJB's SSDJ College of Pharmacy, Chandwad, India from January to June, 2020.

Reagents and diagnostic kits: Streptozotocin was purchased from Sigma-Aldrich, US, virgin coconut oil was freshly prepared in the laboratory using a hot extraction method and curcumin was obtained as a gift sample from ASOJ Soft Caps Ltd., Baroda. Diagnostic kits or the estimation of endogenous antioxidants were purchased from Elabscience, USA.

Dose fixation of curcumin in VCO: For this purpose, 5 mg of curcumin was mixed in 1 mL of VCO using a vortex mixer for 5 min, the mixture was kept overnight and the next day it was centrifuged at 10000 RPM for 30 min. The supernatant was collected and the residue was dried and the quantity of curcumin was weighted. The soluble portion of curcumin was calculated by deducting the final weight from the initial weight. It was observed that 0.165 mg of curcumin is solubilized in 1 mL of VCO. Two doses of VCO i.e., 4 mL and 8 mL/kg were selected and accordingly, the soluble curcumin was measured i.e., 0.66 and 1.32 mg, respectively.

Experimental animals: Male Wistar rats were procured from Wockhardt Ltd., Aurangabad, India and are utilized in the present study. The rats were kept in the animal house and were maintained as per the guidelines provided by committee for the purpose and supervision on experiment in animals. The study was permitted by Institutional Animal Ethics Committee with approval number SSDJ/IAEC/2019-20/03.

Induction of DPN: DPN was induced in the rats by injecting a single dose of STZ (60 mg/kg, i.p.). The rats were monitored for diabetes by the estimation of blood glucose levels. Rats with fasting blood glucose (FBG) of more than 250 mg/dL were considered as diabetes and they were used for further study. The diabetic rats were further monitored for up to four weeks for the development of neuropathic pain. Neuropathic pain was significantly observed after 4 weeks and it was assessed by performing mechanical allodynia using Von Frey hair test. The rats having significant neuropathic pain were then divided into different groups and the treatment was continued for 4 weeks.

Experimental design: Rats were randomly divided into five groups after the development of DPN and each group contained six rats. The treatment was continued for 4 weeks. Group, I served as normal control and received citrate buffer for four weeks. Group II served as DPN rats. Group III received VCO (4 mL/kg, p.o.) for 4 weeks in DPN rats. Group IV and V received VCOSC in low dose (0.66 mg/4 mL/kg, p.o.) and high dose (1.32 mg/8 mL/kg, p.o.) for 4 week in DPN rats.

Assessment of behavioral and biochemical parameters

Estimation of blood glucose levels: Monitoring of blood glucose levels is an important parameter for the confirmation of diabetes. Blood glucose was estimated from the diabetic as

well as treatment rats using a Digital Glucometer (Accu-Chek). Rats with glucose levels of more than 250 mg/dL were considered diabetic.

Assessment of mechanical allodynia (Von Frey test): Rats were kept on the siew of acrylic cage 15 min before the test. Von fray filaments of varying pressure were applied on the plantar surface of the rat paw and the paw withdrawn latency was noted. The test was repeated 6 times in 4-5 sec. About 50% pain threshold was calculated as suggested by Chaplan *et al.*[11].

Assessment of cold allodynia (Acetone test): In this test, the swab soaked with acetone solution was applied on the plantar surface of the paw of rats for 5 sec. Paw withdrawal latency was recorded for each animal[12].

Assessment of mechanical hyperalgesia (Randall-Selitto method): The pressure was applied to the dorsal surface of the rat's paw using the plastic tip of the instrument. The endpoint was noted as compression break in CBK (%) and the test was repeated 2-3 times.

Assessment of heat hyperalgesia (Hot Plate test): Paw withdrawal latency was monitored and recorded as MPE (%), test cut-off time of 20 sec was maintained[13].

Estimation of endogenous antioxidants level: Lipid peroxidation (LPO), the activity of reduced Glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) were estimated using a standard diagnostic kit supplied by Elabscience, USA. The estimation was carried out using the method provided in the kit.

Statistical analysis: All data were expressed as Mean±SEM. Analysis was performed by applying one-way ANOVA followed by Dunnett's multiple comparison tests using GraphPad Prism version 5. The results were considered statistically significant at $^{\#}p<0.05$, compared with the control group. $^{*}p<0.05$, compared with the DPN group.

RESULTS

Effect of VCOSC on body weight, food intake, water intake and blood glucose level: The bodyweight (162.72±2.12 g) of DPN rats was found to be significantly ($^{\#}p<0.05$) decreased as compared to normal control rats (238.28±1.16 g) at the end of 8 weeks. Treatment with VCOSC for 4 weeks showed a dose-dependent and significant ($^{*}p<0.05$) rise in body weight (209.53±3.12 g) as compared to DPN rats (162.72±2.12 g). Treatment with VCO alone did not show any significant changes in body weight in Table 1.

At the end of the treatment period, food intake and water intake were monitored. DPN rats showed a significant ($^{\#}p<0.05$) increase in food intake (89.17±4.52 g) as well as water intake (235.21±1.32 mL) as compared to control rats (42.0±1.56 g and 139.18±2.37 mL). Treatment with VCO alone does not produce significant ($^{*}p<0.05$) changes in both the parameters. VCOSC showed a dose-dependent reduction in the feed intake (60.52±2.36 g) and water intake (174.65±3.21 mL) as compared to DPN rats (89.17±4.52 g and 235.21±1.32 mL) (Table 1).

The blood glucose level in DPN rats was found to be significantly ($^{\#}p<0.05$) increased (302.16±15.87 mg/dL) as compared to normal control rats (119.53±8.07 mg/dL). Rats treated with a low and high dose of VCOSC for four weeks showed a significantly ($^{*}p<0.05$) reduction in serum glucose (168.10±12.77 mg/dL) level as compared to DPN rats. VCO alone didn't show any significant effects on blood glucose levels as compared to DPN rats in Fig. 1.

Effect of VCOSC on behavioural alteration: Mechanical allodynia was evaluated by using Von Frey hair filaments in STZ-induced DPN in a rat's left hind paw. About 50% gram threshold was calculated. It was observed that the 50% gram threshold value of pain is significantly ($^{\#}p<0.05$) decreased (3.116±0.087 g) in DPN rats as compared to control rats (7.066±0.11 g). Treatment with a low and high dose of VCOSC showed significant ($^{*}p<0.05$) recovery (6.067±0.237 g) in pain threshold as compared to DPN rats shown in Fig. 2a.

Table 1: Effect of VCOSC on body weight, feed intake and water intake

	Bodyweight (g)		Feed intake (g)		Water intake (mL)	
Groups	0 week	8th week	0 week	8th week	0 week	8th week
I	230.81±1.86	238.28±1.16	38.67±1.05	42.0±1.56	140.71±2.62	139.18±2.37
II	232.22±1.50	162.72±2.12$^{\#}$	37.67±1.15	89.17±4.52$^{\#}$	140.32±3.21	235.21±1.32$^{\#}$
III	234.85±1.37	184.81±3.22	35.01±1.12	76.83±2.01	139.35±2.36	228.21±2.22
IV	231.12±0.91	198.16±2.22*	39.17±1.42	63.44±3.21*	140.88±3.32	200.21±3.12*
V	232.18±1.66	209.53±3.12*	39.77±1.32	60.52±2.36*	142.25±3.32	174.65±3.21*

Values are expressed as Mean±SEM, one-way ANOVA was followed by Dunnett's t-test, values are considered significant when $^{\#}p<0.05$, compared with the control group and $^{*}p<0.05$ compared with the DPN group

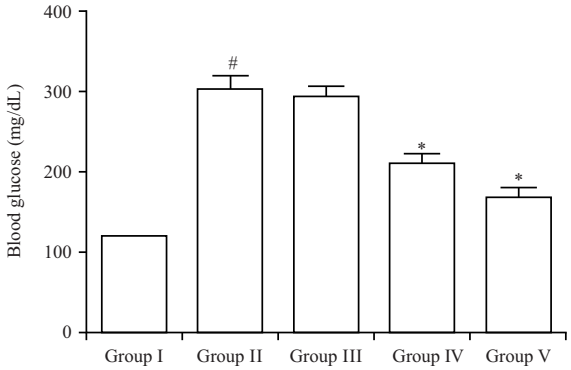

Fig. 1: Effect of VCOSC on blood glucose level

Values are expressed as Mean±SEM, one-way ANOVA was followed by Dunnett's t-test, values are considered significant when #p<0.05, compared with the control group and *p<0.05 compared with the DPN group

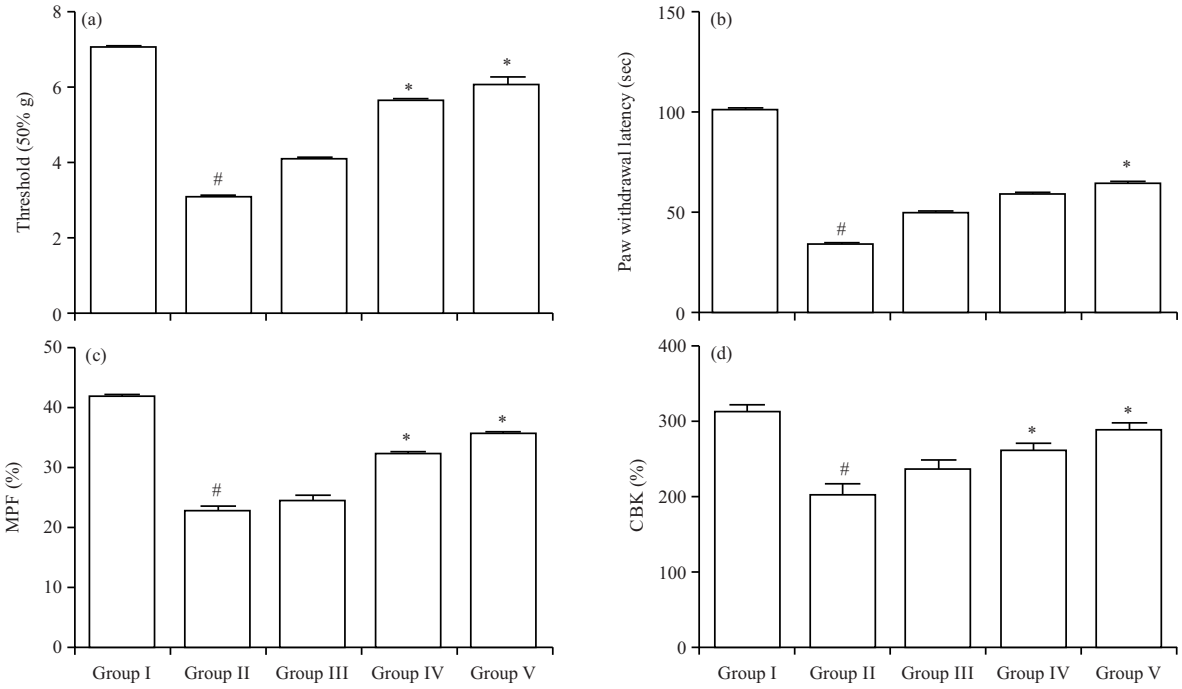

Fig. 2(a-d): Effect of VCOSC, (a) Mechanical allodynia by using Von Frey hair filaments, (b) Cold allodynia by using acetone, (c) Thermal allodynia by using hot plate and (d) Mechanical hyperalgesia

Values are expressed as Mean±SEM, one-way ANOVA was followed by Dunnett's t-test, values are considered significant when #p<0.05, compared with the control group and *p<0.05 compared with the DPN group

Acetone produces cold allodynia. In the present study paw withdrawal latency in second was determined using acetone. Rats with DPN showed a significant (#p<0.05) reduction (33.431±0.940 sec) in paw withdrawal latency compared to normal control rats (100.210±1.08 sec). Treatment with VCOSC at a high dose for 4 weeks displayed a significant (*p<0.05) increase (63.980±2.280 sec) in paw withdrawal latency (33.431±0.940 sec) in rats compared to DPN rats as shown in Fig. 2b.

The results obtained from thermal allodynia using hot plate apparatus and mechanical hyperalgesia are shown in (Fig. 2c and d) rats with DPN showed a significant (#p<0.05) reduction in MPE (%) (22.66±0.881) and CBK (%) (201.95±15.81) as compared to normal control rats (41.66 ±0.86 and 312.28±10.17). Treatment with VCOSC for 4 weeks showed a dose-dependent and significant (*p<0.05) increase in MPE (%) (35.66±0.421) and CBK (%) (288.85±8.90) rats compared to DPN rats (22.66±0.881 and 201.95±15.81).

Table 2: Effect of VCOSC on endogenous antioxidant activity

Groups	SOD (units/mg tissue)	GSH (µg GSH/mg tissue)	CAT (µmoles of H_2O_2 /mg tissue)	LPO (nm MDA/mg tissue)
I	53.7±0.45	40.98±1.20	21.9±1.44	11.79±0.55
II	22.61±0.31#	22.44±0.69#	10.12±4.58#	44.38±0.53#
III	24.89±0.20	28.08±0.44	11.02±6.81	39.54±0.53
IV	37.67±0.73*	33.26±0.56*	11.84±4.41	23.97±0.45*
V	43.41±0.74*	36.56±0.53*	12.09±5.41	19.2±0.35*

Values are expressed as Mean±SEM, one-way ANOVA was followed by Dunnett's t-test, values are considered significant when #p<0.05, compared with the control group and *p<0.05 compared with the DPN group

Effect of VCO solubilized curcumin on endogenous antioxidant level: The level of endogenous antioxidants such as SOD, CAT, GSH and LPO was measured in sciatic tissue homogenate. The level of SOD (22.61±0.31), GSH (22.44±0.69) and CAT (10.12±4.58) were found to be significantly (#p<0.05) decreased in the DPN rats as compared to the normal control rats (53.7±0.45, 40.98±1.20 and 21.9±1.44) whereas the level of LPO was significantly (#p<0.05) increased (44.38±0.53) as compared to control rats (11.79±0.55). Treatment with VCOSC at two different doses showed a significant (*p<0.05) prevention of altered levels of SOD (43.41±0.74), GSH (36.56 ± 0.53) and LPO (19.2 ± 0.35). The level of CAT was not affected by the treatment of VCO alone and both the doses of VCOSC in Table 2.

DISCUSSION

DPN is a secondary common complication of diabetes and occurs in more than 50% of diabetic populations and 40-50% experience chronic pain from DPN[14,15]. In the present study, VCOSC showed better protection in diabetic peripheral neuropathy rather than virgin coconut oil alone. This combination of VCO and curcumin may have synergistic effects or virgin coconut oil may enhance the bioavailability of curcumin. Hyperglycemia is the hallmark of STZ-induced diabetes in rats. It has been reported that administration of STZ to the rats causes the destruction of pancreatic beta-cell and thereby insufficient release of insulin[12], which might be one of the reasons for the elevation of blood glucose levels in the present study. Alteration in body weight, feed intake and water intake was observed in DPN rats[13]. Chronic hyperglycemia may produce a drastic reduction in body weight and an increase in water intake and feed intake. A previous study on STZ-induced diabetes displayed the similar type of results[16], the present results are in line with the reported findings. In the present study, VCOSC significantly reduced the elevated level of glucose in DPN rats. The report showed that curcumin-enriched virgin coconut oil showed better effects than alone curcumin and virgin coconut oil[10]. VCO and curcumin have been reported to reduce elevated glucose levels in diabetic rats[8,17,18].

Pain is characterized by the behavioural pattern of an individual and is considered one of the important characteristics for the evaluation of neuroprotective drugs in DPN. In the present study, the intensity of neuropathic pain was evaluated using thermal and mechanical allodynia and mechanical hyperalgesia. It has been observed that the nociceptive threshold by mechanical allodynia using Von Frey hair was found to be reduced in DPN. The left paw withdrawal latency of rats is also reduced in case of cold allodynia and the MPE (%) is also reduced in thermal hyperalgesia in hot plate apparatus. CBK (%) was found to be significantly decreased in mechanical compression of the paw. The present results are in line with the report presented previously[12]. The changes in nociceptive pattern involve several mechanisms such as the formation of nitrosyl radical, activation of poly (ADP-ribose) polymerase pathway and oxidative stress was thought to be associated with allodynia and hyperalgesia[19]. The treatment with VCOSC for 4 weeks shows significant improvement in the pain threshold. VCO is reported to possess analgesic, anti-inflammatory and strong antioxidant properties[20]. Curcumin is also reported to have strong antioxidant and analgesic activity and is widely used in household purposes and a key ingredient in traditional medicine[17].

In diabetes chronic hyperglycemia causes free radical generation and oxidative stress in the tissue prone to complications of diabetes. A study reported the generation of oxidative stress in streptozotocin-induced DPN[10]. The markers of oxidative stress such as superoxide dismutase, catalase, reduced glutathione and lipid peroxidation were significantly altered in the present study which was in line with a previous report[10,16,21,22]. VCO and Curcumin are reported as powerful antioxidants. The combination of both in the form of VCOSC shows better antioxidant effects compared to individual compounds. This synergistic antioxidant activity may help in preventing the generation of free radicals during DPN and helps in the prevention of pain threshold in rats.

CONCLUSION

In conclusion, streptozotocin administered to rats show DPN by altering various behavioural and oxidative markers. VCOSC protects the changes towards normal as compared to individual treatment groups. This protection might be due to the strong antioxidant and analgesic activity of both compounds. Further, the bioavailability of curcumin may be enhanced in presence of virgin coconut oil.

SIGNIFICANCE STATEMENT

The study provides the use of dietary components, which are used on daily basis by society and may be helpful in the prevention of complications like neuropathy. The outcome of the study reflects the combination of curcumin and virgin coconut oil imparts more beneficial effects compared to alone.

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