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Original Article

NEUROPROTECTIVE AND ANTINOCICEPTIVE EFFECT OF CURCUMIN IN DIABETIC NEUROPATHY IN RATS

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ABSTRACT

The present study reports the preventive effects of Curcumin against the progression of diabetic neuropathy in STZ induced diabetic rats.Curcumin (200 mg/kg body weight) was orally administered to STZ induced diabetic rats for 3 weeks. Metformin (150mg/kg body weight) was used as reference drug. Tail flick test, Hot plate test, Allodyniaand Rota-rod tests were conducted to record nociceptive and motor co-ordination changes at different time intervals i.e., 2nd and 3rd week. Nerve conduction velocity was recorded. Aldose reductase, Cyclooxygenase, Prostaglandin peroxidase and Na + K + ATPase activity were determined after 3 weeks. Histopathological evaluations of sciatic nerve were also performed. Curcumin treatments to diabetic rats for 21 days significantly reduced plasma glucose content. Curcumin increased tail flick latency significantly in diabetic rats. It also showed its protection against nociceptive behaviour in hot plate test and allodynia test. NCVs were also attenuated by treatment of curcumin. The significant decrease in AR shows its protection against diabetic complications. Decreased Cyclooxygenase, Prostaglandin peroxidase suggests its protections against inflammation and pain. Progressive morphological alterations induced by diabetes in sciatic nerve were protected with Curcumin treatment. The results of nociceptive, motor, conduction velocity, histological and biochemical markers indicate the protective anti-nociceptive, anti-inflammatory and neuroprotective properties of Curcumin in preventing the progression of diabetic neuropathy.

Keywords: Nociception, Curcumin, Diabetic neuropathy,Aldose reductase, Nerve conduction velocity, Cyclooxygenase, Prostaglandin peroxidase.

INTRODUCTION

Diabetes mellitus is one of the most widespread chronic diseases in the world. One of the most frequently occurring microvascular complications is diabetic neuropathy, with clinically significant morbidities characterised by pain, foot ulcers and amputations [1]. The primary risk factor for diabetic neuropathy is hyperglycemia. Although through dietary changes, hypoglycemic agents, insulin, and islet transplantation there have been major advances in the control of hyperglycemia (diabetes), but the long-term complications of diabetic neuropathy remains a serious problem. There are various proposed mechanisms that explain the pathophysiology of diabetic complications. These mainly include oxidative stress, increased polyol pathway,osmotic stress, increased formation of advanced glycation end products, activation of protein kinase C and increased hexosamine pathway flux [2]. The oxidative stress is a major determinant in diabetic complication including diabetic neuropathy which is a result of cross link between aforesaid pathways[2, 3, 4]. Therefore, agents or compounds that exert multiple actions, such as antioxidant, antidiabetic/hypoglycemic, AR inhibition, and antiglycation properties could be more effective than agents with a single action.Cyclooxygenases catalyze the conversion of Arachidonic acid to prostaglandins and thromboxane; its inhibition will result in management of acute pain and inflammatory pain [5].

Curcumin the major yellow phenolic curcuminoid present in turmeric has been reported to have a wide range of biological activitiesincluding antihyperglycemic, antioxidant and anti-hypolipidemic [6]. Neuroprotective, anti-inflammatory [7] and anti-aging effects were also shown in rat brain [8]. Curcumin is neuroprotective in multiple animal models and has great potential for the prevention or treatment of age-related dementia arising from Alzheimer's disease [9,10] or cardiovascular disease, Parkinson's disease, other diseases of aging and aspects of aging itself [11]. The pharmacological safety and efficacy of curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseases. This study reports the possible protective effects of curcumin on serum glucose, sciatic neuronal proteins, neuronal protein carbonyls, nociceptive, motor coordination, nerve condution velocity, Aldose reductase COX, PG peroxidase and Na^+K^+ATPase activity.

MATERIAL AND METHODS

Experimental Animals

Adult male albino rats of Wistar strain (NIN) aged 11–12 weeks and weighing between 160±20 gms, were used for this study. The animals were maintained in the climate-controlled animal facility (Dept. of Zoology, Osmania University, Hyderabad) with a 12-h light/12 h dark cycle at a stable temperature 18-22 ⍰C. The animals were fed with standard pellet diet (NIN) and tap water *adlibitum*; Corn cob was used as bedding material. All institutional guidelines of the Institutional Animal Ethics Committee were strictly adhered to in the care and treatment of the animals used throughout the study (CPCSEA No, 383/01/a/CPCSE).

Chemicals used

Curcumin was commercially obtained from Hi-media, INDIA. STZ was obtained Sigma Chemical (USA).Metformin drug procured from Hetero drugs, INDIA. Other essential chemicals were obtained from SRL biochemical, INDIA

Experimental design

About 30 rats were starved for 24 h and divided into control and experimental groups. Each experimental rat for diabetes was injected with Streptozocin at the dosage of 50 mg/Kg body weight in 100mM Citrate buffer pH 4.5. The experimental animals randomly assorted into five groups with six animals for each group, were treated as follows:

Group-I: These animals were treatedwith physiological saline, served as control

Group-II: The STZ-induced diabetic animals, served as diabetic

Group-III: The STZ induced diabetic animals treated with Metformin drug, served as Met+D (150mg/kg body weight in RO water)

Group-IV: The STZ induced diabetic animals treated with Curcumin (200mg/kg body weight in RO water) served as Cur+D

Group-V: Control animals treated with Curcumin(200mg/kg body weight in RO water), served as Cur+C. The animals were sacrificed by cervical dislocation after 21 days; biochemical and histological studies were conducted on sciatic nerve.

The parameters studied

Analgesic tests such as tail-flick test[12], hot-plate test [13], allodynia test [15],Randall and Selitto, 1957 [16] [17], Neuro-muscular coordination test [18] [19],NCV[20] were conducted on all experimental rats. The percentage antinociception was calculated for both tail-flick test and hot-plate test by the formula according to Ipe Ninan and Kulkarni, 1999 [14].

Biochemical estimations

Preparation of tissue extracts

The animals were sacrificed by cervical dislocation after 21st day and sciatic nerves were carefully dissected out avoiding extraneous tissue, washed with normal saline, blotted dry, the nerves were immediately transferred and kept at 80 ⍰C to be used later.10% tissue (Sciatic nerve) homogenate was prepared in 50mM potassium phosphate buffer pH 7.2 and centrifuged at 25,000g for 30 min at 4°Cand the supernatant is used for aldose reductase (AR) activity.

Biochemical parameters studied.

Aldose reductase activity [21],Na^+K^+ATPase activity [22] [23],Blood glucose (GOD-POD) method, Neural proteins[24], Neural protein carbonyl [25], COX [26], PG peroxidase [27]

Histological processing

Nerve samples were fixed in a solution of 2.5% purified glutaraldehyde and 0.5% saccarose in 0.1 M Sorensen phosphate buffer, pH 7.4, for 6–8 h, then washed and stored in 1.5% saccarose in 0.1 M Sorensen phosphate buffer at 4–68C prior to embedding. Before embedding the nerves were washed in 1.5% saccarose in 0.1 M Sorensen phosphate buffer for a few minutes and then immersed for 2 h in 2% osmium tetroxide (Sigma) in the same buffer solution.The specimens were then dehydrated with numerous alcohol passages (starting from 30% and graduating to absolute ethanol) and embedded in wax. Semi thin transverse sections 5- to 7- inches thick were cut using microtome and stained with Toluidine blue [28].

Statistical analysis

Results are presented as mean ± S.E., of six in each group. Statistical difference between control and various groups was determined by multiple comparison of ANOVA. *p*-values less than 0.05 were considered significant.

RESULTS

The body weights, serum glucose levels, neural proteins and protein carbonyls of all the experimental groups with diabetes are shown in Fig 1, Fig.2, Fig.3 and Fig.4. STZ induced diabetes in rats resulted in significant (46%) decrease in the body weight on 21st day with age-matched controls. There was no increase in the final body weight in the Met+D group as well as Curcumin treated animals. STZ-induced diabetes in rats resulted in(169%) increase in the blood glucose levels on 21st day in comparison to the control group which was restored to (43%) in metformin treated animals and 66% in Curcumin treated animals.

The total neural protein levels of sciatic nerve from diabetic group on 21st day showed a significant decrease (p <0.05) as compared to that of control and the treated groups. Levels of protein carbonyls an important marker of the long-term AGE's state was found to be significantly elevated in (p <0.05) diabetic animals compared to age-matched control. The protein carbonyls levels in Cur+D group was decreased by (-60%) compared to control group. (Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05.Significance Control Vs Diabetes is <0.005; Control Vs Met+D is <0.77; Diabetes Vs Cur+D is <0.562; Diabetes Vs Cur+C is <0.282; Met+D Vs Cur+D is <0.003; Met+D Vs Cur+C is < 0.001;Cur+D Vs Cur+C is < 0.621; Cur+C Vs Diabetes is < 0.285; Cur+C Vs Met+D is < 0.011).

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05.Significance Control vs Cur+c is < 0.426; Met+D Vs Cur+D is < 0.010 respectively).

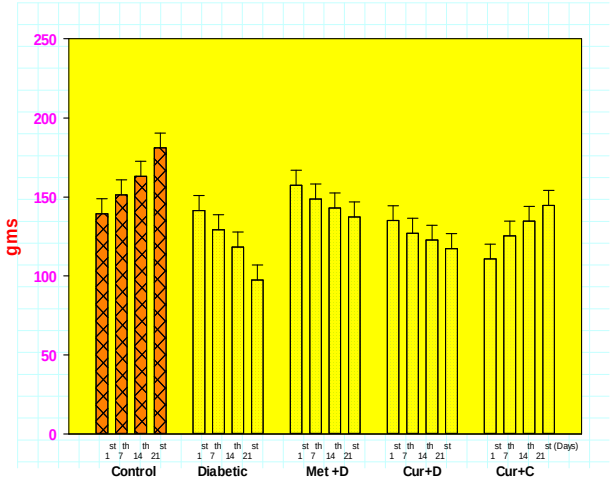


Fig. 1: Changes in Body weights on treatment with Curcumin. (Body weight in grams)

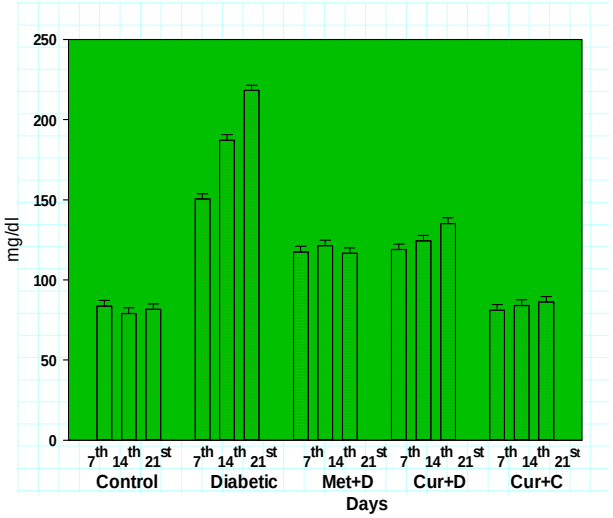


Fig. 2: Changes in the serum glucose levels on treatment with Curcumin. (Serum glucose levels expressed in mg /dl)

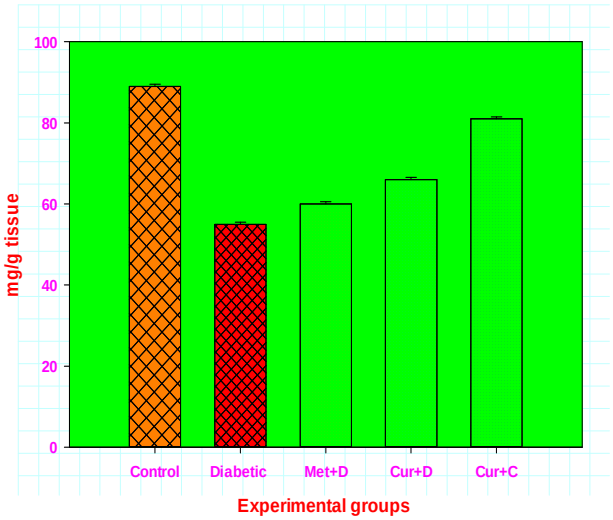


Fig. 3: Changes of level of proteins in sciatic nerve on treatment with Curcumin. (Proteins expressed in mg/gram tissue)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05. Significance Diabetes Vs Met+D is <0.01 respectively).

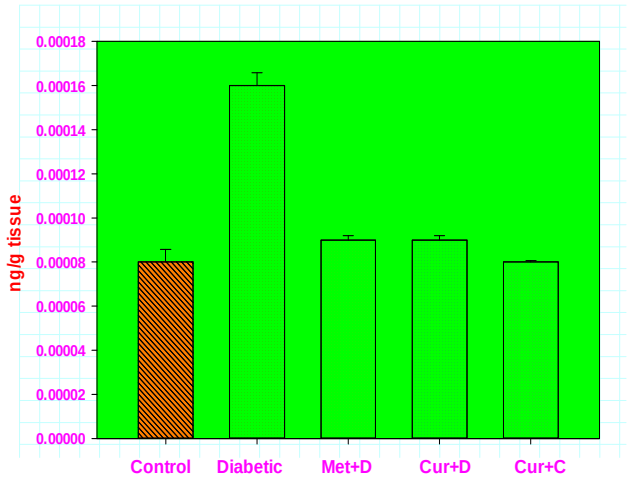


Fig. 4: Changes in level of protein carbonyls in sciatic nerve on treatment with Curcumin. (Protein carbonyls are expressed in ng/gram tissue)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05.Significance Control Vs Diabetes is <0.006; Control Vs Met+D is <0.329; Control Vs Cur+D is <0.329; Diabetes vs Met+D is <0.04; Diabetes Vs Cur+D is <0.04; Diabetes vs Cur+C is <0.04; Met+D Vs Cur+C is < 0.3 respectively).

Measurement of antinociceptive activity

The nociceptive threshold was significantly lower in diabetic rats as compared to control in Tail flick test (Fig.5), Hot plate test (Fig.6) and allodynia test (Fig.7).

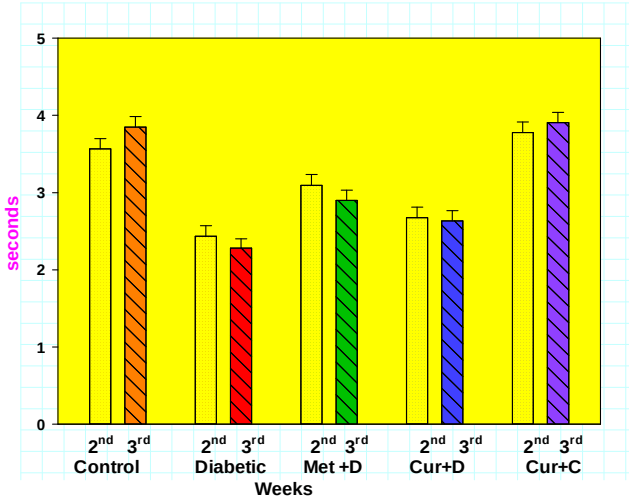


Fig. 5: Changes of tail flick test latency on treatment with Curcumin. (Tail flick latency is expressed in seconds)

Hyperalgesia was evident in the tail flick test and hot plate test at 2nd week (P<0.005), maximum decrease in pain threshold was observed at 3rd weeks after STZ injection in rats as compared to non-diabetic control rats. Curcumin administration to diabetic rats resulted in time dependent increase in pain threshold level as compared to untreated diabetic rats. Mechanical nociceptive threshold as indicated by Randall Selitto Pain test (Fig.8), measured on 14th and 21st day was significantly (p<0.05) decreased in STZ induced hyperglycemic rats indicating mechanical hyperalgesia when compared to Controls. The mechanical threshold levels after metformin (STZ induced diabetic rats) treatment resulted in marginal reversal of latency on 14th day. The Cur+D treatment has shown a similar trend of regaining the mechanical thresholds better than met group on 14th and 21st day respectively. The treatment with Curcumin ascends antinociceptive activity in progressive STZ induced diabetic neuropathy. The STZ induced diabetic rats has shown progressive decrease in coordination with the time periods, as shown in Fig.9. The decrease in coordination was moderate on 14th day which further declined in the coordination indicating neuropathy on 21st day. The subsequent treatment with Curcumin was found to reverse the coordination on 14th day and 21st day respectively. The percentage of antinociception of tail flick test and hot plate test are shown in table.1. (Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05. Significance control Vs Cur+c is <0.321; Diabetes Vs Cur+D is <0.035; Met+D Vs Cur+D is < 0.016; Cur+D Vs Diabetes is < 0.035 respectively).

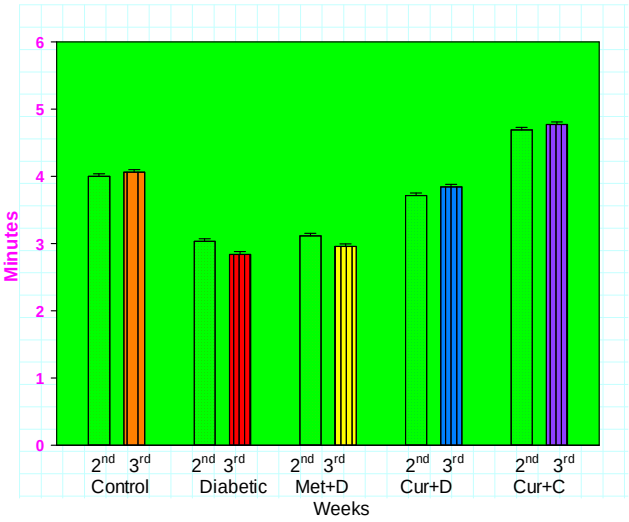


Fig. 6: Changes of Hot plate test latency on treatment with Curcumin. (Hot plate latency is expressed in minutes)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05. Significance Diabetes vs Met+D is < 0.018 respectively]

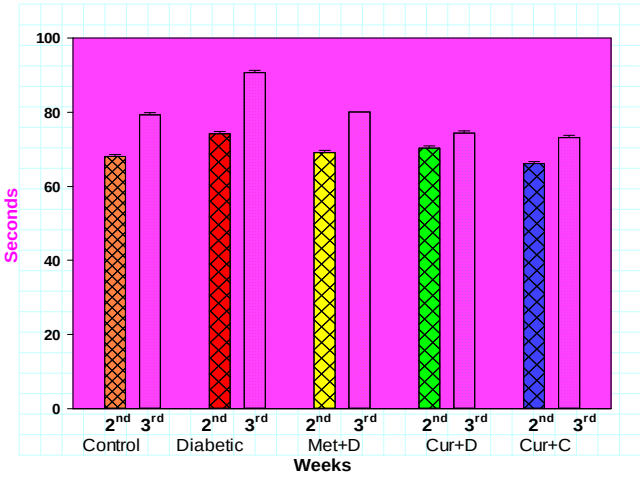


Fig. 7: Changes of Allodynia test latency on treatment with Curcumin. (Allodynia latency is expressed in seconds)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05 Significance Control Vs Met+D is < 0.129; Met+D Vs Cur+D is < 0.001; Control vs Cur+D is <0.032 respectively).

Nerve conduction velocity

Diabetic rats showed 27% lower NCV thancontrol on 21st day (Fig. 10). Curcumin treatment of Diabetic rats (Cur+D) resultedin (17%) lower NCV compared to control. However, the NCV of Diabetic rats treated with metformin (Met+D) was (22%) lower than control. There was no significant different in NCV of control animals treated with Curcumin.

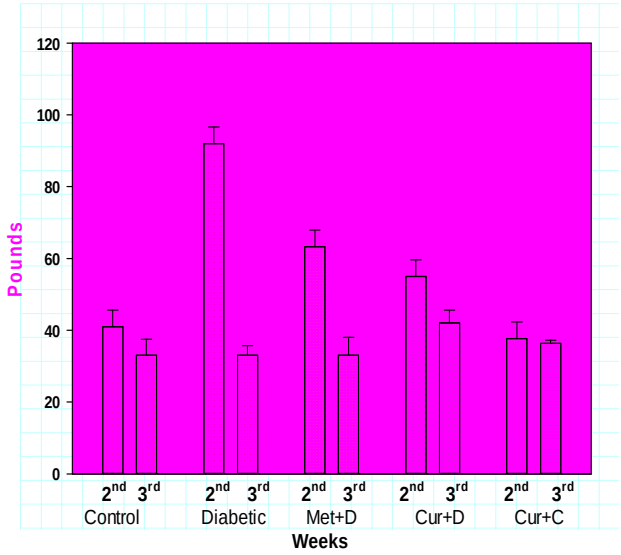


Fig. 8: Changes in Randall Selitto Pain test latencies on treatment with Curcumin. (Pain is expressed in pounds)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05 Significance control Vs Met+ D is< 0.004; Control Vs Cur+D is < 0.050; Control Vs Cur+C is <0.618; Diabetes vs Met+D is < 0.001; Met+D Vs Cur+D is < 0.223; Met+D Vs Cur+C is < 0.002 respectively)

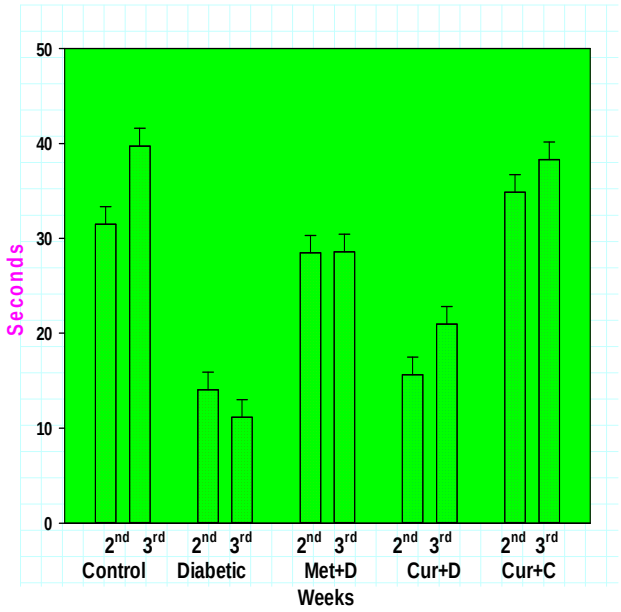


Fig. 9: Changes in Neuromuscular coordination on treatment with Curcumin. (Coordination test is expressed in seconds)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05. Significance Control Vs Met+D is < 0.01; Control Vs Cur+C is < 0.609; Diabetes Vs Cur+D is <0.005 respectively)

Table 1: Changes in percentage of antinociception in Tail flick test and Hot plate test on treatment with Curcumin.

Experimental groups	Tail flick test 2nd 3rd week	Hot plate test 2nd 3rd week
Con Vs Diabetes	17 20	6.26 7.85
Con Vs Met+D	7.36 12.44	5.88 7.16
Con Vs Cur+D	13.83 19.78	1.75 1.09
Con Vs Cur+C	3.31 0.92	0.82 0.94

(The values expressed in percentage)

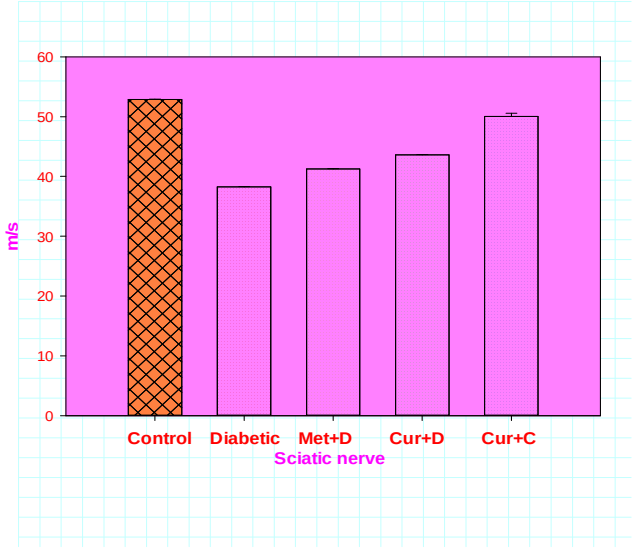


Fig. 10: Changes in Nerve conductionvelocity on treatment with Curcumin. (NCV expressed in meters/sec).

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05)

Aldose reductase and Na^+-K^+ ATPase activity of sciatic nerve

There was significant increase in aldose reductase enzyme activity in sciatic nerve of diabetic animals on 21st day (+50%) as compared to controls. Diabetic rats treated with curcumin showed decrease in aldose reductase activity by 18% (Fig. 11). Percentage of variation of metformin treated diabetic was (61%) and that of control animals treated with curcumin was (11%). Sciatic nerve Na^+-K^+ ATPase activity (Fig. 12) was significantly reduced in diabetic rats (-77%) as compared to normal control. This was largely reversed by curcumin treatment by (-6%).

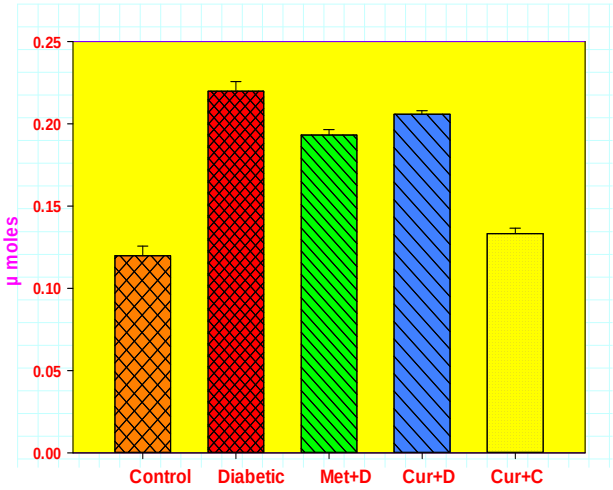


Fig. 11: Changes in AR activity of sciatic nerve on treatment with Curcumin. (Expressed as µ moles of NADPH oxidized/ hour/100 mg of protein)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at p<0.05 Significance Diabetes vs Cur+C is< 0.2 respectively).

Cyclooxygenase and Prostaglandin Peroxidase activity in Sciatic nerve

In STZ induced diabetic rats a significant (p<0.05) increase in Cyclooxygenase activity was observed in Sciatic nerve (+130.42%) on 21st day when compared to the control group (Fig.13). The Cyclooxygenase activity was predominantly recovered in Sciatic

nerve (+95.76%) of diabetic animals when treated with metformin. Curcumin treatment of diabetic rats has shown gradual recovery of Cyclooxygenase activity in sciatic nerve (+55.61%). Prostaglandin Peroxidase activity was significantly ($p<0.05$) increased in sciatic nerve on 21st day by (+262.2%) in STZ induced diabetic rat when compared to controls (Fig.14). Metformin treatment of diabetic rats showed decreased activity of PG peroxidase in sciatic nerve by +93%. However the PG peroxidase activity in sciatic nerve is partially regained by (+110%), when diabetic animals treated with Curcumin.

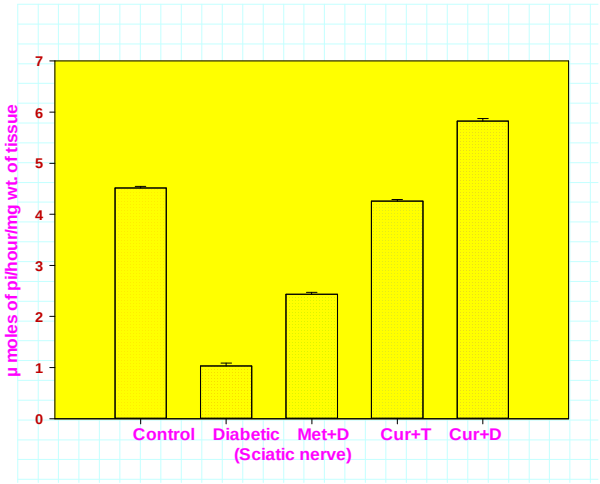


Fig. 12: Changes in Na^+K^+ATPase activity of Sciatic nerve on treatment with Curcumin. (Expressed as µ moles of pi/ hour/mg wt. of tissue)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at $p<0.05$)

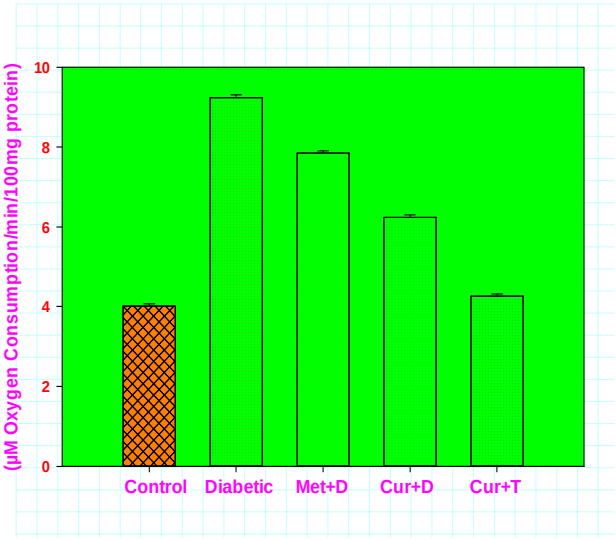


Fig. 13: Effect of Curcumin on Cyclooxygenase (COX) activity of sciatic nerve in Control and Experimental group of Rats on 21st day. (Expressed as µM Oxygen Consumption/min/100mg protein/1ml)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at $p<0.05$ Significance Control vs Diabetes is ns, Control Vs Met+D is ns; Control Vs Cur+C is <0.02; diabetes vs met is ns; diabetes vs cur+D is <0.02; diabetes vs Cur+C is ns respectively)

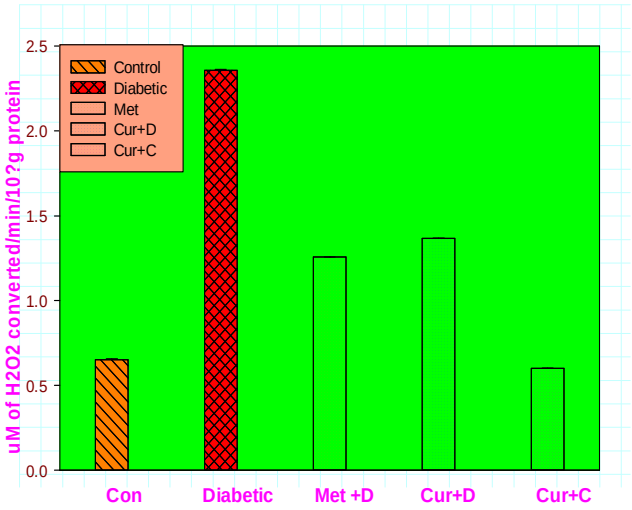
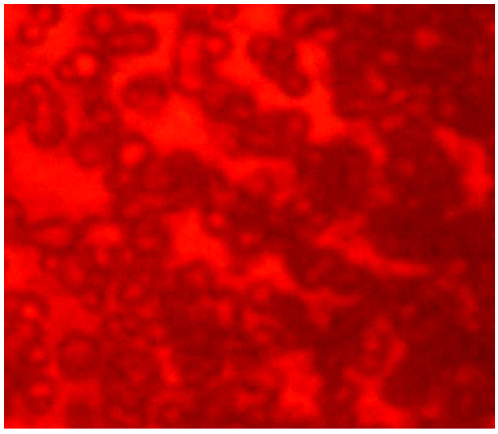


Fig. 14: Effect of Curcumin on Prostaglandin Peroxidase (PG peroxidase) of sciatic nerve in Control and Experimental group of Rats on 21st day. (Expressed as µ M of H_2O_2 converted /min/10 µg protein)

(Values are given as mean ± SE for groups of six animals each. Values are statistically significant at $p<0.05$ Significance control vs diabetes is ns, con Vs met is ns; con vs Cur+D is ns ;con vs Cur+c is <0.001; diabetes vs met is ns; diabetes vs cur+D is ns; diabetes vs Cur+C is ns respectively)



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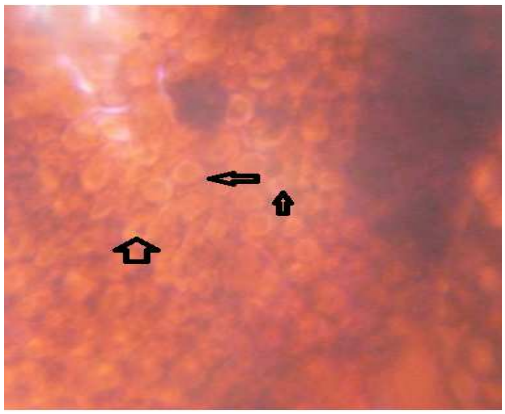

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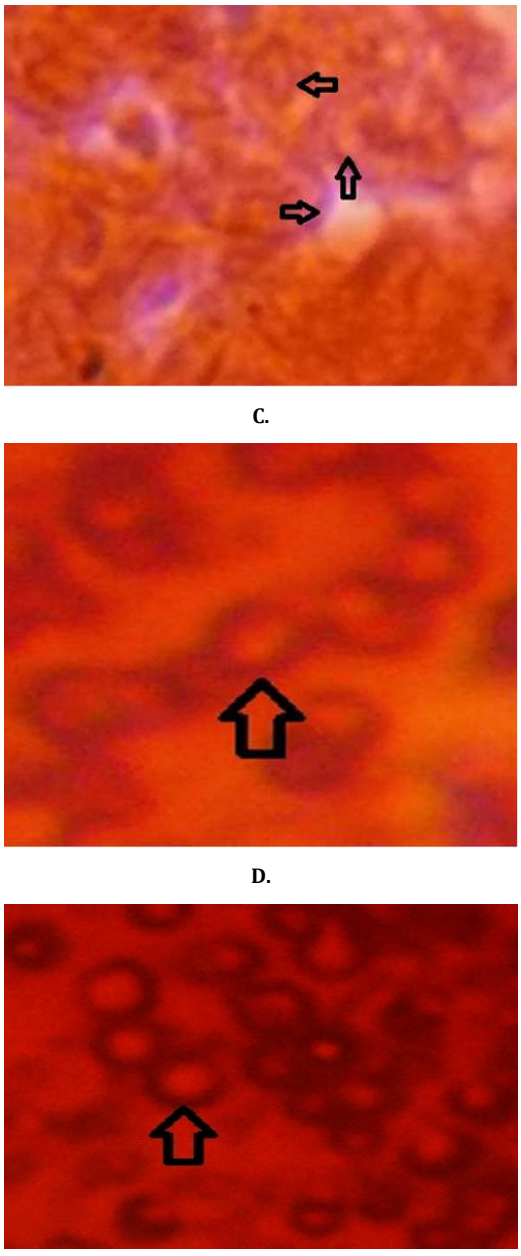

C.

D.

E.

Fig. 15: Histological changes in Sciatic nerve

Fig.15Photomicrographs showing the Transverse sections of the sciatic nerves. Fig. A is of Control rat (5µm thick, 100X+Immersion oil) showing normal histological features with thick myelin membrane. B is the photomicrograph of T.S of Sciatic nerve of STZ-induced diabetic rat, showing axonal atrophy (swelling), and Increased extra-axonal space among nerve fibres (↑), deposition of electron dense material within the axons. In Fig.C STZ-induced diabetic rats treated with metformin (5µm thick, 100X+Immersion oil) showed onion bulb formation (→) and also segmental demyelination. STZ-induced diabetic rats treated with Curcumin (Cur+D) are shown in Fig.D, no demyelination and no onion bulb formation is seen and also myelin membrane is intact (↑). Control animals treated with Curcumin have not shown any significant histological changes (Fig.C).

DISCUSSION

Diabetes mellitus is chronic metabolic disorder with late complicationsuch as diabetic neuropathy and is frequently painful, with the pain involving predominantly the distal extremities. Pain associated withdiabetic neuropathy can occur either spontaneously or as aresult of exposure to only mildly painful stimuli (hyperalgesia)or to stimuli not normally perceived as painful (allodynia)[29].Diabetic neuropathic pain is widely regarded to be caused byperipheral neuropathy.The primary cause of diabetic neuropathy is thought to be hyperglycaemia. STZ induced rats spontaneously show, within weeks of onset, acute significant decreases in nerve conduction velocities (NCVs) [30], which are associated with increased activity of the polyol pathway [31]and impairments of neural Na+/K+-ATPase[32]. Simultaneously, structural changes start to emerge consisting of axonal atrophy in a length-dependent manner and eventually axonal dying-back degeneration [33].

In the present study, Curcumin attenuated sciatic nerve effect of STZ induced Hyperglycemia effects and also nociceptive and motor coordination behaviour. The behavioural alterations started on 7th day after the STZ-induced diabetes in rats and lasted throughout the experimental period showing hyperalgesia. These observations are in line with earlier findings. [34,35]. Neuropathic pain associated with peripheral nerve injury is characterized by the sensory abnormalities such as unpleasant abnormal sensation (dysesthesia), an increased response to painful stimuli (hyperalgesia), and pain in response to a stimulus that does not normally provoke pain (allodynia) [36].Spontaneously diabetic mice with hyperglycemia have shown a decreased sensitivity to the antinociceptive effects of morphine [37]. Administration of Metformin and Curcumin, resulted in significant increase in TFT, HPLs and consequent decrease was observed in allodynia response, compared to diabetic rats suggesting reduction of hyperalgesic condition. It was reported a higher level of pain threshold in STZ-Diabetic male rats in hot plate response [38]. The hyperalgesic response in the tail withdrawal test is generally attributed to central mechanisms, whereas the hyperalgesic response on the hot plate is considered to result from a combination of both central peripheral mechanisms. Generation of superoxide due to oxidative stress in diabetes may be responsible for vascular and neuronal complications of painful neuropathy [39]. The increase in the thresholds of pain to thermal stimuli by Curcumin may be due to its antioxidant effect that may contribute to its protective action against lipid peroxidation and enhance effect on cellular antioxidant defense [40].The loss of motor coordination is a common characteristic of many neurological disorders and is one of the most readily observable effects of diabetic neuropathy. Motor coordination is a complex behavioural domain, and can reflect balance, muscle strength, and patterned gait, as well as sensory competence. The loss of motor coordination was removed with the curcumin treatment.

The Randall – Selitto test is used to measure the anti-inflammatory and analgesic properties of substances [41]. The sensitivity to pain reaction is increased by increased inflammation which is elevated by non-narcotic and narcotic analgesics. Sensitivity to pain is increased by prostaglandin and other inflammatory mediators. The curcumin increased the threshold to the diabetes induced pain threshold suggest that their anti-inflammatory activity may involve interfering with the arachidonic metabolic pathway or the activity of the arachidonic bye products and/or other inflammatory mediators.

The key electrophysiological findings of the present study were to report that Curcumin have prevented a diabetes induced deficit in NCV. This protection occurred in line with that of obvious alteration in the biochemical indexes measured, which included Na^+-K^+-ATPase activity,, and polyol pathway enzyme such as AR. Altered polyol metabolism and an associated decrease in neuronal myo-inositol content were reported to be associated with diabetes [42]. This finding suggests that lower tissue myo-inositol concentrations may result in abnormal neuronal Na^+-K^+-ATPase activity through a reduction in the formation of diacylglycerols and inositol trisphosphate and incomplete activation of the sodium pump by activated protein kinase C [43, 44, 45]. Lower Na^+-K^+ ATPase activity may underpin the depressed NCV in diabetes [45].

The conversion of glucose to sorbitol, which is catalysed by aldose reductase in the presence of NADPH, may be related to the

protection against oxidative stress and abnormalities in nitric oxide action [46]. Under normoglycemic conditions, polyol pathway accounts for approximately 3% of glucose utilization [47], whereas more than 30% of glucose is metabolized through this pathway under hyperglycemia [48]. Elevated polyol pathway flux, decrease NADPH levels, impairing GSH redox cycle [49], which is an important mechanism of cell protection against oxygen derived free radicals. These free radicals are markedly increased in diabetes and, if not scavenged, they cause damage to the vascular endothelium and neutralize nitric oxide [49].The AR activity was attenuated by treatment with Curcumin which may be due its hypoglycemic activity [8] which allows little glucose available for polyol pathway by main normal glycolytic pathway and also may be due to its antioxidant activity [8] which neutralises whatever free radicals generated due to diabetes. Instead, depletion of Na^+-K^+ ATPase activity [50] of STZ induced diabetic rats was significantly reduced compared to control rats on 21st day. Curcumin treatment restored the Na^+-K^+ ATPase activity. It might be possibly improved by inhibition of oxidative stress [51] and also by amelioration of vascular function [52]. COX-1 and COX-2 play important role of Arachidonic acid metabolic pathways in diabetes. Prostaglandins play a vital role in neuropathic pain.COX-1 protein expression was reported unchanged in the diabetic peripheral nerve [53], whereas COX-2 protein expression was increased in diabetic peripheral nerve [53, 54]. Selective COX-2 inhibitors were reported to prevent motor nerve conduction and endoneurial nutritive blood flow deficits, peripheral nerve oxidative stress and inflammation [54, 55], in diabetic rats. Diabetic COX-2 deficient mice were protected from MNCV and SNCV slowing, intraepidermal nerve fiber loss, and oxidative damage that were clearly manifest in the diabetic wild-type mice [55]. The Cyclooxygenase (COX) activity and Prostaglandin Peroxidase activity were clearly attenuated by treatment with Curcumin which may play essential role in anti-inflammatory action.

Activation of the polyol pathway is an early and important mechanism in Diabetic Neuropathy. Shunting of excessive glucose through this pathway leads to intracellular accumulation of sorbitol and fructose, creating osmotic stress leading to axonal swelling. This will result in compensatory depletion of other organic osmolytes like myo-inositol and taurine. The restoration of structural alterations seen with the Curcumin treatment may be attributed by maintaining normal glucose metabolism. Thereby increased utilization of glucose via glycolysis may be suggested in sciatic nerve. In diabetic condition there will be decreased utilization of glucose through glycolysis. As glucose is freely permeable to nerve tissue [56,57], there is accumulation of glucose in sciatic nerve which is metabolized, via the activated sorbitol pathway enzymes aldose reductase (AR) having high *K*m for glucose and sorbitol dehydrogenase (SDH), to sorbitol and fructose whose accumulation in the nerves is known to be implicated in the development of long-term diabetic complications.

CONCLUSION

The studies of Nociception, motor coordination and NCV are considered as remarkable markers for validating antinociceptive effect of Curcumin in STZ induced Wistar rats**.** There is significant decrease in levels of AR, Na K ATPase, COX, PG peroxidasein treated groups indicating the protective role of Curcumin against STZ induced alteration.

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