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ASSESSMENT OF EFFECT OF *CORDIA DICHOTOMA* ON STREPTOZOTOCINE INDUCED DIABETIC NEUROPATHY ON RATS

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ABSTRACT

Cordia dichotoma belonging to the family Boraginaceae. *Cordia dichotoma* is commonly present in tropical and subtropical regions. It grows in the sub-Himalayan tract and outer ranges, ascending up to about 1 500 m elevation. It is found in divers of forests ranging from the dry deciduous forests of Rajasthan to the moist deciduous forests of Western Ghats in India and tidal forests in Myanmar. Several chemicals have been identified from seeds of *C. dichotoma*. The seed contains α-amyrins, betulin, octacosanol, lupeol-3rhamnoside, β-sitosterol, β-sitosterol-3glucoside, hentricontanol, hentricontane, taxifolin-3-5-dirhamnoside, hesperitin-7-rhamnoside and Fatty acids such as palmitic acid, stearic acid, arachidic acid, behenic acid, oleic acid and linoleic acid. Four flavonoid glycosides (robinin, rutin, rutoside, datiscoside and hesperidin), a flavonoid aglycone (dihydrorobinetin) and 2 phenolic derivatives (chlorogenic acid and caffeic acid) were isolated from seeds. Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage have no symptoms. Others may have symptoms such as pain, tingling, or numbness loss of feeling in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs. The present study was performed to evaluate the potency and effect of ethanolic extract of *Cordia dichotoma* in Diabetic neuropathy. Thus, it can be concluded from our findings that the levels of Glucose, total serom protein, urine protein levels, which are actually raised in Diabetic neuropathy can be lowered with Ethanolic extract of *Cordia dichotoma*. Two doses were given to chosen animal model and dose at 200mg/kg has shown its significant effect. Further studies on the extract and/or its chemical constituents are needed to pinpoint the findings. This report may serve as a footstep on this aspect and conclusion.

Keywords: *Cordia dichotoma*, Rats, Nerve, Muscle, Blood Glucose, Protein.

INTRODUCTION

Diabetes is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

The World Health Organization (WHO) Expert Committee on Diabetes in 1980 and, later, the WHO Study Group on Diabetes Mellitus endorsed the substantive recommendations of the NDDG (Ford, 2005). These groups recognized two major forms of diabetes, which they termed insulin-dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes), but their classification system went on to include evidence that diabetes mellitus was an etiologically and clinically heterogeneous group of disorders that share hyperglycemia in common.

There are several distinct disorders, most of them rare, in which glucose intolerance is a feature. There are large differences in the prevalence of the major forms of diabetes among various racial or ethnic groups worldwide (Spanakis and Golden, 2013). Patients with glucose intolerance present with great phenotypic variation; take, for example, the differences between thin, ketosis-prone, insulin-dependent diabetes and obese, nonketotic, insulin-resistant diabetes.

Evidence from genetic, immunological, and clinical studies shows that in western countries, the forms of diabetes that have their onset primarily in youth are distinct from those that have their onset mainly in adulthood (Leslie *et al.,* 2021). A type of non-insulin-requiring diabetes in young people, inherited in an autosomal dominant fashion, is clearly different from the classic acute-onset diabetes that typically occurs in children. In tropical countries, several clinical presentations occur, including diabetes associated with fibrocalcific pancreatitis.

Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage have no symptoms (Gooch and Podwall, 2004). Others may have symptoms such as pain, tingling, or numbness loss of feeling in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs.

Diabetic neuropathies are neuropathic disorders that are associated with diabetes mellitus. These conditions are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum) in addition to macrovascular conditions that can culminate in diabetic neuropathy. Relatively common conditions which may be associated with diabetic neuropathy include third nerve palsy; mononeuropathy; mononeuropathy multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy (Sima *et al.,*1997).

Cordia dichotoma belonging to the family Boraginaceae. *Cordia dichotoma* is commonly present in tropical and subtropical regions. It grows in the sub-Himalayan tract and outer ranges, ascending up to about 1 500 m elevation. It is found in divers of forests ranging from the dry deciduous forests of Rajasthan to the moist deciduous forests of Western Ghats in India and tidal forests in Myanmar (Jamkhande *et al.,* 2019). In Maharashtra, it grows in moist monsoon forest. It does not grow gregariously, but is found growing singly in moist shady ravines and valleys.

The species is widespread in the Philippines and found in thickets and secondary forests at low and medium altitudes. It also distributed Southern China and Formosa and throughout other like Peninsular Malaysia to tropical Australia and Polynesia. The species is propagated by seeds.

Several chemicals have been identified from seeds of *C. dichotoma*. The seed contains α-amyrins, betulin, octacosanol, lupeol-3rhamnoside, β-sitosterol, β-sitosterol-3glucoside, hentricontanol, hentricontane, taxifolin-3-5-dirhamnoside, hesperitin-7-rhamnoside and Fatty acids such as palmitic acid, stearic acid, arachidic acid, behenic acid, oleic acid and linoleic acid. Four flavonoid glycosides (robinin, rutin, rutoside, datiscoside and hesperidin), a flavonoid aglycone (dihydrorobinetin) and 2 phenolic derivatives (chlorogenic acid and caffeic acid) were isolated from seeds. The significant anti-inflammatory activity of seeds is because of α-amyrins and taxifolin-3-5-dirhamnoside (71.4%, 67.8% respectively). The seeds also contain fatty acids and flavonoids (Jamkhande *et al.,* 2013).

MATERIALS AND METHODS

Collection & authentication: - The leaves of *Cordia dichotoma* has been taken from local market, authenticated by Dr. S. K. Tiwari, department of botany, Dr. H.S. Gour University, Sagar (M.P.). Herbarium no. Bot./Her./2023 and reference no. 2023/Bot./166.

Extraction Method

Petroleum ether: Defatting is required for the removal of fatty constituents and pigments. The shad dried coarse powder of leaves were packed in extraction thimble of soxhlet apparatus and subjected to continuous hot extraction with petroleum ether for 18 hour or till the clear extraction was obtained. The extract was filtered while hot and resultant extract was distilled in vacuumed under reduced pressure in order to remove the solvent completely. It was dried and kept in the dessicator till the experimentation. Obtained extract was weighed and percentage yield were calculated in terms of air dried powdered crude material.

Ethanol extract: Mark left after petroleum ether dried below 50^0C (hot air oven) and then packed well in extraction thimble of soxhlet apparatus and subjected to continuous hot extraction with petroleum ether for 18 hour or till the clear extraction was obtained. The extract was filtered while hot and resultant extract was distilled in vacuumed under reduced pressure in order to remove the solvent completely (Hierro *et al.,* 2021). It was dried and kept in the dessicator till the experimentation. Obtained extract was weighed and percentage yield were calculated in terms of air dried powdered crude material.

Mature Sprague-Dawley rats (200–225gm) were taken from the animal house of SIPS, Sagar. All animal were kept in standard plastic polypropylene cages with stainless steel coverlids and wheat straw was used as bedding material (Al-Amin *et al.,* 2006). The animal were facilitated with standard environment of photoperiod (12:12 hr dark: light cycle) and room temperature (23 ± 2^0 C). The animal assists free to feed and purified water ad libitum. All experiment was according to CPCSEA (SIPS/EC/2023/57) guidelines. Animals fast for overnight and streptozotocin (STZ; 65 mg/kg) in 0.02 M citrate saline buffer were administered intraperitoneally. The age-matched control

group received citrate buffer only. Blood glucose levels were monitored every week. Rats with blood glucose levels ≥15 mM (200 mg/dl) for 2 consecutive weeks was considered diabetic.

Description of groups

Control Group (Vehicle Treated)

Negative Control (Disease Induced)

Standard STZ+ (Metformin+ Pioglitazone+ Glimepiride) + Amitriptylin

Test group-1 (STZ+Ethanolic Extract of *Cordia dichotoma* 100mg/kg)

Test group-II (STZ+Ethanolic Extract of *Cordia dichotoma* 200mg/kg)

RESULTS AND DISCUSSION

Pharmacological Screening

Body Weight

Diabetic neuropathy results in loss of body weight. Decrease in the body weight due to derangement of metabolic pathways is a common feature in diabetes (Furman, 2015). The body weight of control rats was progressively increased (135±3.56 gm to 147±2.57 gm) whereas there was a significant decrease in the body weight (140±3.55 gm to 95±3.78 gm) of STZ induced diabetic rats, which might be due to the breakdown of tissue proteins. Diabetic rats treated with dose of *Cordia dichotoma* from 14th day at 100mg/kg and 200mg/kg shows no weight gain, indicating the beneficial effect of the *Cordia dichotoma*.

Muscle Grip Strength

Presence and severity has been shown to be associated with decrease muscle strength in Diabetic neuropathy (Shin *et al.,* 2017). In the present study, significant improvement in motor behavior, in particular grip strength after treatment of diabetic animals with *Cordia dichotoma* has been observed. As per treatment, showed significant increase in grip strength, at dose of 100mg/kg (25.5± 1.335 to 42.67±1.085) and 200mg/kg (26±1.461 to 51.37±1.085) when compared with diabetic control group, where significant decrease in grip strength (23.5±1.31 to 8.16±0.894) was observed in negative control group (diabetic group).

Thermal Pain Sensitivity

Hyperalgesia is a constant feature of sensory dysfunction in spontaneously and experimental model of Diabetic neuropathy, Observation indicted that improvement in hot plate response that is pain threshold of diabetic animal with *Cordia dichotoma* (George *et al.,* 2007). The response with that group was found to be better than other groups of treatments. The analgesia was near normal with standard group and with *Cordia dichotoma*. Significant increase in pain threshold was observed in *Cordia dichotoma*. This conforms the usefulness of ethenolic extract of *Cordia dichotoma* in symptomatic treatment of painful diabetic neuropathy. Significant increased in pain threshold capacity were observed at dose of 100mg/kg (10.23± 0.81 to 7.34± 0.78) and 200mg/kg (11.66± 0.81 to 6.38± 0.91) compared with negative control group.

Blood Glucose Level

Blood glucose level is an index for the diagnosis of diabetic neuropathy. Hyperglycaemia is an important factor in the development and progression of the complications of diabetic neuropathy (Prasad *et al.,* 2009)**.** In the present study, diabetic rats showed elevation in blood glucose level (85±2.46mg/dl to 247±2.43mg/dl) which

upon oral administration of ethanolic extract of *Cordia dichotoma* resulted in a significant reduction of blood glucose level (P>0.001) dose of 100mg/kg (205±2.64 mg/dl to 168±2.34 mg/dl) and 200mg/kg (210±3.48 mg/dl to 152±2.34 mg/dl), indicating the beneficial effect of the *Cordia dichotoma*.

Total Serum Protein

The level of total serum protein was found to decrease in diabetic group of rats (5.35±0.43gm/dl to 2.34±0.32gm/dl) and urine protein level was found to be increased (2.15±0.026 to 3.47±0.023gm/dl) (Kumar *et al.,* 2006). The deficiency of insulin leads to defective amino acid/protein metabolism, which may be a more important factor than hyperglycaemia in the etiology of some diabetic complications, because of that, protein excretion from the urine may be increased [14]. During our present study, upon oral administration with *Cordia dichotoma* resulted in a significantly inhibits proteolysis caused by insulin deficiency and thus increased the levels of total serum proteins at the dose of dose of 100mg/kg (3.75±0.26gm/dl to 4.25±0.37gm/dl) and 200mg/kg (3.72±0.24gm/dl to 4.58± 0.38gm/dl), and also decreased the excretion of protein through the urine at dose of 100mg/kg (2.26± 0.028 to 0.98± 0.026mg/dl) and 200mg/kg (2.27± 0.070 to 0.93± 0.060mg/dl) indicating the beneficial effect of the *Cordia dichotoma*.

Animal Model: STZ Induce Diabetes Type 2

Group	Average body weight (gm)					
	0 day	7 day	14 day	21 day	28 day	35 day
V.C.	135±3.56	140±3.22	137±4.38	145±2.56	145±2.38	147±2.57
N.C.	140±3.55	132±3.24	125±3.35	115±3.67	108±3.54	95±3.78
Std	135±3.47	130±3.26	123±3.98	118±3.45***	120±3.46***	120±3.34***
T1	135±3.43	127±3.55	120±3.76	115±3.28**	110±3.36**	110±3.46**
T2	138±3.45	130±3.28	123±3.78	115±3.32***	115± 3.48***	115± 3.26***

Table no. 1. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

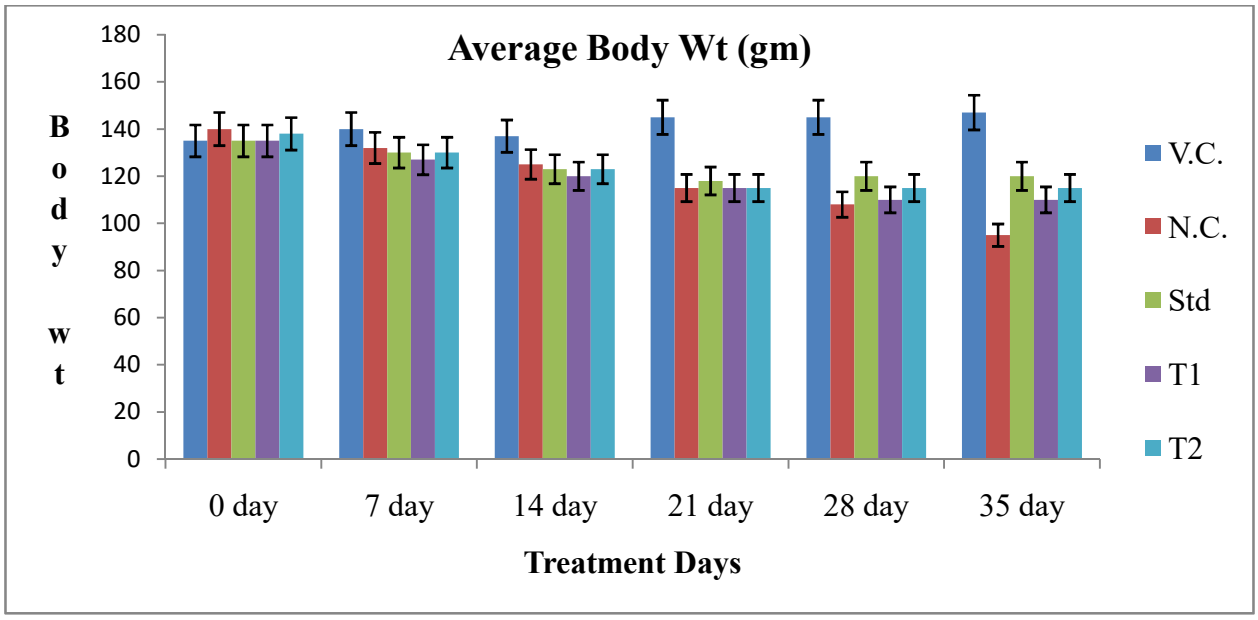

Fig. 1. Body weight. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II(*Cordia dichotoma* 200mg/kg).

Groups	Muscle Grip Strength (sec.)					
	0 day	**7 day**	**14 day**	**21 day**	**28 day**	**35 day**
V.C.	60±4.683	63.5± 2.683	61.38± 2.671	59± 3.176	65± 4.638	63± 3.581
N.C.	59.33±3.029	34± 1.862	23.5± 1.310	17.67± 1.116***	12.5± 1.147***	8.16± 0.894***
Std	58.17± 4.262	33± 2.683	22.67± 0.843	28.83± 0.872***	39.83±0.83***	40± 0.954***
T1	58.5± 2.907	34.5±1.893	25.5± 1.335	28.33± 0.980**	35.28±1.493**	37.67±1.085**
T2	57.17± 3.673	33.17±2.167	26±1.461	30.67± 1.145***	35.70±1.493***	38.37± 1.085***

Table no. 2. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

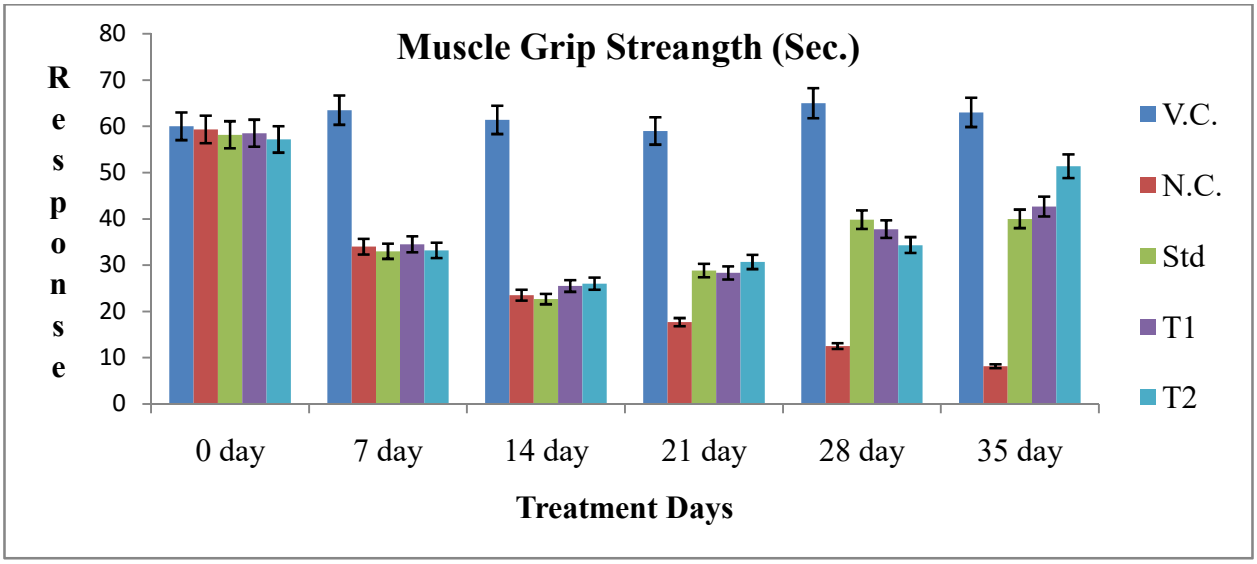

Fig. 2. Muscle Grip Strength. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II(*Cordia dichotoma* 200mg/kg).

Groups	Thermal Pain Sensation (Sec.)					
	0 day	**7 day**	**14 day**	**21 day**	**28 day**	**35 day**
V.C.	5.33± 0.51	5.5± 0.54	5.45± 0.54	5.66± 0.51	5.83± 0.75	5.68± 0.78
N.C.	5.5± 0.54	8.5± 0.61	11.65± 1.03	12.50± 0.83	12.66± 1.03	13.67± 1.38
Std	5.33±0.51	8.38± 0.83	10.45± 1.03	8.16± 0.75***	6.2± 0.98***	6.13± 1.38***
T1	5.65± 0.65	8.66± 0.51	10.23± 0.81	8.2± 1.22**	7.83± 0.51**	7.34± 0.78**
T2	5.5± 0.54	8.33± 0.51	11.66± 0.81	7.85± 0.75***	7.23± 0.63***	6.38± 0.91***

Table no. 3. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

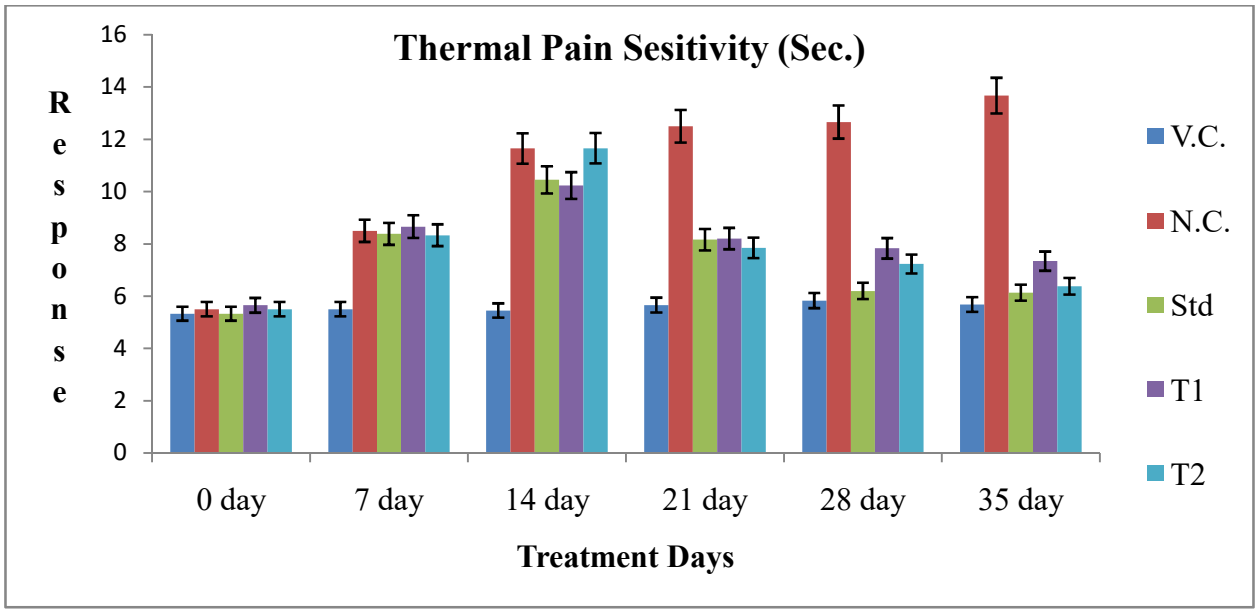

Fig. 3. Thermal Pain Sensitivity. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II(*Cordia dichotoma* 200mg/kg).

Group	Blood Glucose Level (mg/dl)					
	0 day	**7 day**	**14 day**	**21 day**	**28 day**	**35 day**
V.C.	83±2.45	85±3.15	85±2.38	83±4.10	85±2.36	85±2.39
N.C.	85±2.46	154±3.45	208±2.76	215±3.94	228±2.76	247±2.43
Std	85±2.53	153±3.55	207±2.73	187±3.86***	172±2.64***	148±2.54***
T1	83±2.45	157±3.62	205±2.64	180±3.76***	175± 2.35**	168± .34**
T2	85±2.38	155±3.64	210±3.48	172± 4.26***	165± 2.53***	152±2.34***

Table no. 4. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

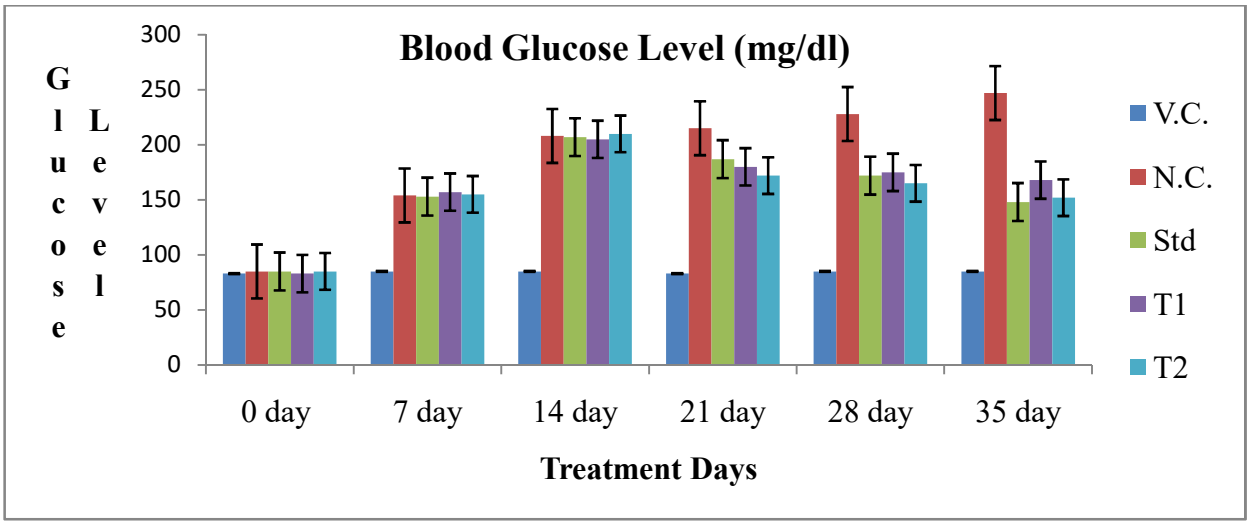

Fig. 4. Blood Glucose Level. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II(*Cordia dichotoma* 200mg/kg).

Group	Total protein in serum (gm/dl)					
	0 day	**7 day**	**14 day**	**21 day**	**28 day**	**35 day**
V.C.	5.37±0.31	5.38±0.15	5.32±0.32	5.31±0.36	5.31±0.31	5.32±0.34
N.C.	5.35±0.43	4.75±0.23	3.82±0.28	3.27±0.31	2.54±0.36	2.34±0.32
Std	5.36±0.32	4.74±0.22	3.78±0.23	3.91±0.32***	4.08±0.36***	4.95±0.35***
T1	5.36±0.35	4.72±0.18	3.75±0.26	3.63±0.35**	3.78±0.38**	4.25± 0.37**
T2	5.32±0.36	4.68±0.21	3.72±0.24	3.75±0.38***	3.84±0.42**	4.58±0.38***

Table no. 5. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

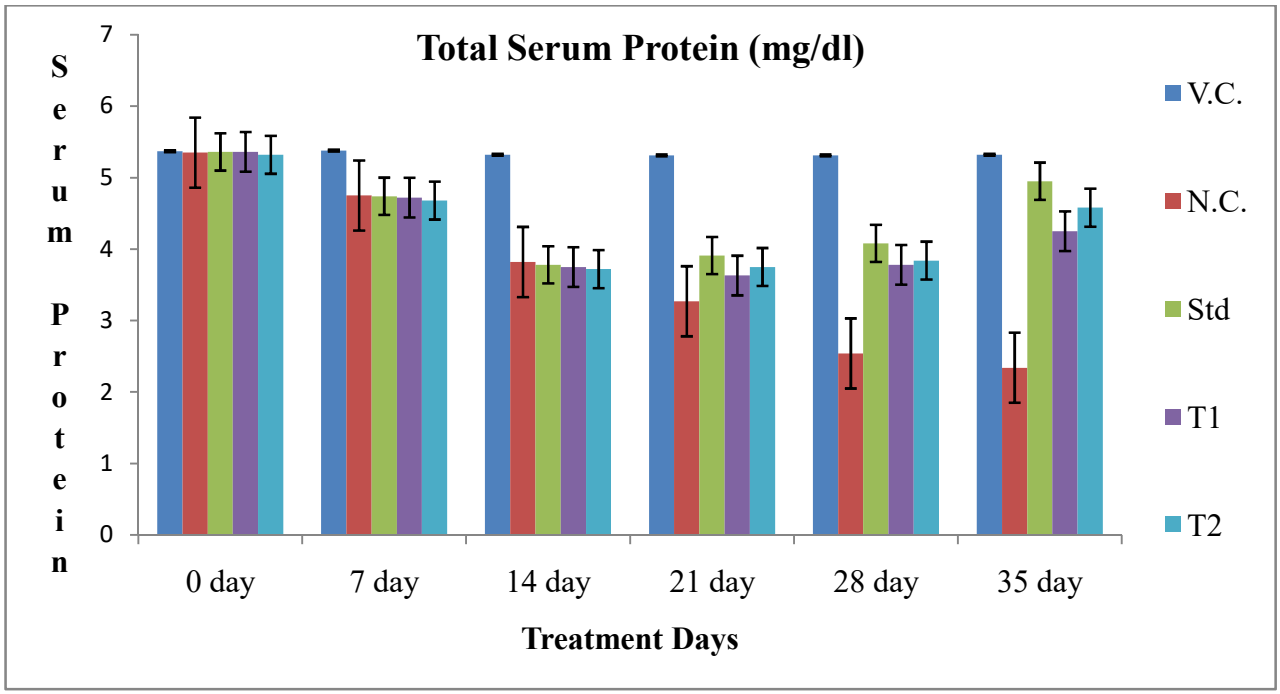

Fig. 5.Total Serum Protein. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II (*Cordia dichotoma* 200mg/kg).

Urine Protein

Groups	Protein Level in Urine (mg/dl)					
	0 day	**7 day**	**14 day**	**21 day**	**28 day**	**35 day**
V.C.	0.27± 0.014	0.25± 0.018	0.30± 0.021	0.26± 0.052	0.25± 0.010	0.25± 0.042
N.C.	0.24± 0.035	1.76± 0.032	2.15± 0.026	2.89± 0.009	3.09± 0.017	3.47± 0.023
Std	0.23± 0.046	1.79± 0.025	2.24± 0.012	1.43± 0.008***	1.23± 0.034***	1.09± 0.007***
T1	0.3± 0.024	1.85± 0.019	2.26± 0.028	1.35± 0.008**	1.05± 0.009**	0.98± 0.026**
T2	0.30± 0.027	1.91± 0.047	2.27± 0.070	1.26± 0.017***	1.01± 0.046***	0.93± 0.060***

Table no. 6. V.C.- Vehicle Treated Group, N.C.- Negative Control Group, Std- Standard Group, T1- *Cordia dichotoma* (100mg/kg), T2- *Cordia dichotoma* (200mg/kg).Values are expressed MEAN±SEM, n=6, ** = P>0.01, *** = P>0.001 when compared to normal control group, a*** = P>0.001 when compared to negative control group.

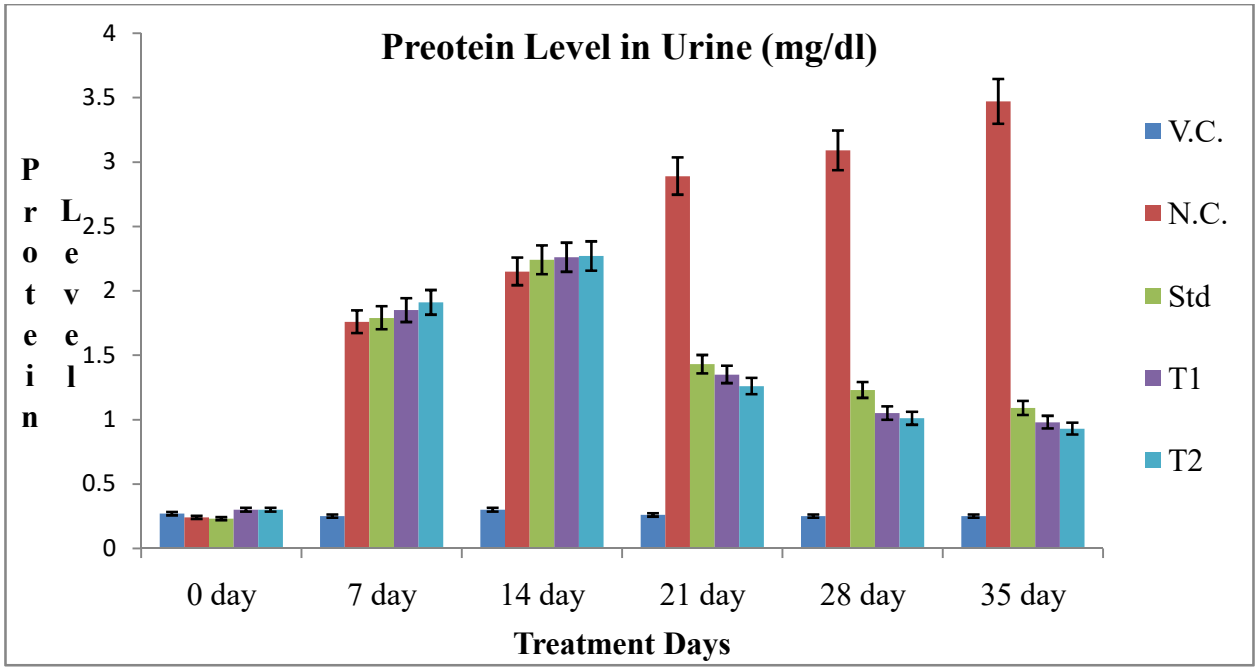

Fig. 6. Urine Protein Level. V.C.- Vehicle Treated Control Group, N.C.- Negative Control Group, Std- Standard Group, T1- Test group I (*Cordia dichotoma* 100mg/kg), T2- Test group II(*Cordia dichotoma* 200mg/kg).

CONCLUSION

In conclusion, the significant effect of *Cordia dichotoma* in diabetic neuropathy in rat was observed, significant effect could be result of synergistic/potentiative action of its drug, since they contain a diverse array of active principles which are able to target multiple mechanisms involved in the pathophysiology of diabetic neuropathy. The ethenolic extract of *Cordia dichotoma* showed no weight gain, increased in grip strength and pain sensitivity. This indicates its protective role against neurons. In summary, *Cordia dichotoma* treatment reversed the alteration in biochemical parameters.

The present study was performed to evaluate the potency and effect of ethanolic extract of *Cordia dichotoma* in Diabetic neuropathy. Thus, it can be concluded from our findings that the levels of Glucose, total serom protein, urine protein levels, which are actually raised in Diabetic neuropathy can be lowered with Ethanolic extract of *Cordia dichotoma*.

Two doses were given to chosen animal model and dose at 200mg/kg has shown its significant effect. Further studies on the extract and/or its chemical constituents are needed to pinpoint the findings. This report may serve as a footstep on this aspect and conclusion.

ACKNOWLEDGMENT

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DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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