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Evaluation of Euphorbia milii Leaves Extract in Diabetic Neuropathic Pain in rats

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Abstract: *Diabetes mellitus is a chronic metabolic disorder leading to various complications, including diabetic neuropathy (DN), characterized by nerve damage and neuropathic pain. This study aimed to evaluate the effect of methanolic extract of* Euphorbia milii *(MEEM) leaves on diabetic neuropathic pain in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced in Sprague Dawley rats via STZ injection (60 mg/kg). Diabetic neuropathy was confirmed after STZ induction in negative control group assessing thermal hyperalgesia using the tail flick test and motor coordination deficits using the rota rod apparatus. Diabetic rats were then treated orally with MEEM at low (100 mg/kg) and high (200 mg/kg) doses, and glibenclamide (5 mg/kg) as a standard control. The effects of MEEM on pain threshold (tail flick latency) and motor coordination (rota rod falling time) were evaluated. Phytochemical screening of MEEM revealed the presence of alkaloids, carbohydrates, cardiac glycosides, tannins, proteins and amino acids, phenolic compounds, flavonoids, anthraquinones, saponins, and terpenoids. The results demonstrated that STZ-induced diabetic rats exhibited significant thermal hyperalgesia and impaired motor coordination compared to normal control rats. Treatment with both low and high doses of MEEM significantly improved tail flick latency and rota rod falling time in diabetic rats compared to the untreated diabetic group. These findings suggest that* Euphorbia milii *leaves extract possesses potential analgesic and neuroprotective effects in the context of diabetic neuropathic pain in rats*

Keywords: *Euphorbia milii*, Diabetic Neuropathy, Neuropathic Pain, Rats, Streptozotocin, Tail Flick Test, Rota Rod Test, Phytochemicals

I. INTRODUCTION

Diabetes mellitus, a prevalent chronic metabolic disorder marked by persistent hyperglycemia, arises due to insufficient insulin production or ineffective insulin utilization. The resultant metabolic disturbances lead to a spectrum of acute and chronic complications, significantly impacting patient morbidity and mortality.[1] Among the long-term complications, diabetic neuropathy (DN), a progressive nerve damage affecting the peripheral nervous system, is a major concern, affecting up to 50% of diabetic individuals.[7] DN manifests in various forms, with diabetic neuropathic pain (DNP) being a particularly debilitating symptom characterized by spontaneous pain, hyperalgesia, and allodynia.[8] The underlying pathophysiology of DNP is complex and involves hyperglycemia-induced oxidative stress, inflammation, axonal damage, demyelination, and alterations in pain signaling pathways.[9] Current treatments for DNP often provide limited relief and are associated with significant side effects. This necessitates the exploration of novel therapeutic strategies, including those derived from natural sources.[13]

Euphorbia milii (Crown of Thorns), a plant belonging to the *Euphorbiaceae* family, has been traditionally used in various cultures for its medicinal properties, including wound healing, treatment of skin conditions, inflammation, pain relief, and fever reduction.[17] Phytochemical investigations of *E. milii* have revealed the presence of various bioactive compounds such as beta-sitosterol, cycloartenol, triterpenes, flavonoids, phenolic acids, alkaloids, and terpenoids. These constituents are known to possess antioxidant, anti-inflammatory, and analgesic properties.[15] Given the complex pathophysiology of DNP involving oxidative stress and inflammation, the phytochemical profile of *E. milii* suggests its potential utility in alleviating neuropathic pain associated with diabetes.

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This study aimed to evaluate the effect of methanolic extract of *Euphorbia milii* (MEEM) leaves on experimentally induced diabetic neuropathic pain in rats. The study assessed the impact of MEEM on thermal hyperalgesia and motor coordination deficits, two key indicators of diabetic neuropathy.

II. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals and reagents used during study

Petroleum Ether, Methanol, Chloroform, Streptozotocin, Molish's Reagent, Mayers Reagent, Sulphuric Acid, Lead Acetate, Ferric Chloride, α – Napthol, Glacial Acetic Acid, Ninhydrin solution, Ammonia solution, Glucose Diagnostic Kit.

2.1.2 Experimental Animals:

Healthy Sprague Dawley rats (8 weeks old, weighing 150-250 gm) were housed under standard laboratory conditions (temperature 22 ± 2°C, humidity 55-60%, 12-hour light/dark cycle) with free access to standard pellet diet and water. All experimental procedures were approved by the Institutional Animal Ethical Committee (IAEC) with reference no. 650/PO/Re/S-2002/2025/CPCSEA/09 and conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

2.1.3 Apparatus and Instruments

Cooling centrifuge, Semiautomatic Biochemistry auto-analyzer, Desiccators, Micropipette, Digital weighing balance and Glass wares, Glucometer.

2.2 Method

2.2.1 Plant Material and Extraction:

Fresh leaves of *Euphorbia milii* were collected from the local area of Yavatmal, Maharashtra, India, and authenticated by a botanist (Reference No. VNCABT/Ytl/Hort/1880/2024). The leaves were shade-dried, coarsely powdered, and subjected to Soxhlet extraction using petroleum ether to remove fatty components, followed by maceration in methanol. The methanolic extract was concentrated by evaporation at 40°C.

2.2.2 Phytochemical Screening:

The methanolic extract of *Euphorbia milii* leaves (MEEM) was subjected to qualitative phytochemical screening using standard procedures to detect the presence of various secondary metabolites, including alkaloids, carbohydrates, cardiac glycosides, tannins, proteins and amino acids, phenolic compounds, flavonoids, anthraquinones, saponins, and terpenoids.

2.2.3 Induction of Diabetes:

Diabetes was induced in rats (except the normal control group) by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 60 mg/kg body weight, dissolved in freshly prepared ice-cold citrate buffer (0.1 M, pH 4.5).[36] Negative control rats received an equivalent volume of citrate buffer. Blood glucose levels were measured using a glucometer (Ambica Diagnostic) 72 hours post-STZ injection, and rats with fasting blood glucose levels ≥ 150 mg/dL were considered diabetic.

2.2.4 Experimental Groups:

The rats were divided into five groups (n=4 per group):
Group 1 (Vehicle Control): Non-diabetic rats treated with normal saline.
Group 2 (Negative Control): Diabetic rats treated intraperitoneally with STZ (60mg/kg)
Group 3 (Low Dose MEEM): Diabetic rats treated orally with MEEM (100 mg/kg).
Group 4 (High Dose MEEM): Diabetic rats treated orally with MEEM (200 mg/kg).

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Group 5 (Standard): Diabetic rats treated intraperitoneally with glibenclamide (5 mg/kg).

2.2.5 Assessment of Diabetic Neuropathic Pain:

A. Thermal Hyperalgesia (Tail Flick Test):

Thermal hyperalgesia was assessed using the tail flick test. Rats were gently restrained, and the distal third of the tail was exposed to a radiant heat source (analgesiometer). The latency of tail withdrawal (flicking) from the heat stimulus was recorded. A cut-off time of 10 seconds was set to prevent tissue damage.[41] Measurements were taken at baseline (day 0), day 3, day 28, and day 42.

B. Motor Coordination (Rota Rod Test):

Motor coordination and muscle strength were assessed using a rota rod apparatus. Rats were placed on a rotating rod (25 rpm), and the time they remained on the rod before falling was recorded (mean falling time, MFT). Each rat was given three trials with an interval of 30 minutes, and the average falling time was calculated.[42] Measurements were taken at baseline (day 0), day 3, day 28, and day 42.

2.2.6 Statistical Analysis:

All data were expressed as the mean ± standard deviation. For statistical Analysis of the rats, group mean were compared by one-way (ANOVA) followed by Dunnett's test, $p<0.01$ was considered as significant value.

III. RESULTS

3.1 Phytochemical Screening:

Phytochemical screening of the methanolic extract of *Euphorbia milii* leaves revealed the presence of alkaloids, carbohydrates, cardiac glycosides, tannins, proteins and amino acids, phenolic compounds, flavonoids, anthraquinones, saponins, and terpenoids (Table 1).

Table No. 1: Phytochemicals Screening of MEEM

Sr. No.	Phytochemicals	Test Performed	Extract Results
1	Alkaloids	Mayer's test	+
2	Carbohydrates	Molish's test	+
3	Cardiac glycosides	Keller-killani test	+
4	Tannins	Braymer's test	+
5	Proteins and Amino acids	Ninhydrin test	+
6	Phenolic compounds	Lead acetate test	+
7	Flavonoids	Ammonia test	+
8	Anthraquinones	Borntrager's test	+
9	Saponins	Foam test	+
10	Terpenoids	Salkowski's test	+

Figure No.1: Phytochemicals screening of methanolic extract of *Euphorbia milii*

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3.2 Effect of MEEM on Body Weight and Blood Glucose Levels:

Table No 2: Evaluation of body weight of rats on day 0, 3, 28 and 42.

Group	Weight of rats on day 0 (gm)	Weight of rats on day 3 (gm)	Weight of rats on day 28 (gm)	Weight of rats on day 42 (gm)
Normal control	218.75 ± 15.67	221.50 ± 12.26	218.50 ± 19.89	227.25 ± 13.94
Negative control	216.50 ± 20.87^{ns}	175.50 ± 6.18**	148.75 ± 6.24**	137 ± 6.88**
Low dose	222.50 ± 15.15^{ns}	174.25 ± 4.11^{ns}	172.75 ± 11.12$^{@}$	179 ± 6.27$^{@@}$
High dose	214.75 ± 16.32^{ns}	171.75 ± 1.71^{ns}	198.50 ± 7.19$^{@@}$	195 ± 17.66$^{@@}$
Standard dose	215.75 ± 20.89^{ns}	191.50 ± 5.80$^{@}$	210.25 ± 8.38$^{@@}$	213 ± 7.87$^{@@}$

The result were expressed as Mean ± SD (n = 4)

^{ns} (*not significant)* = $p>0.05$, $^{**}p<0.01$ when compared to normal control group of rats

^{ns} (*not significant)* = $p>0.05$, $^{@}p<0.05$, $^{@@}p<0.01$ when compared to negative control group of rats

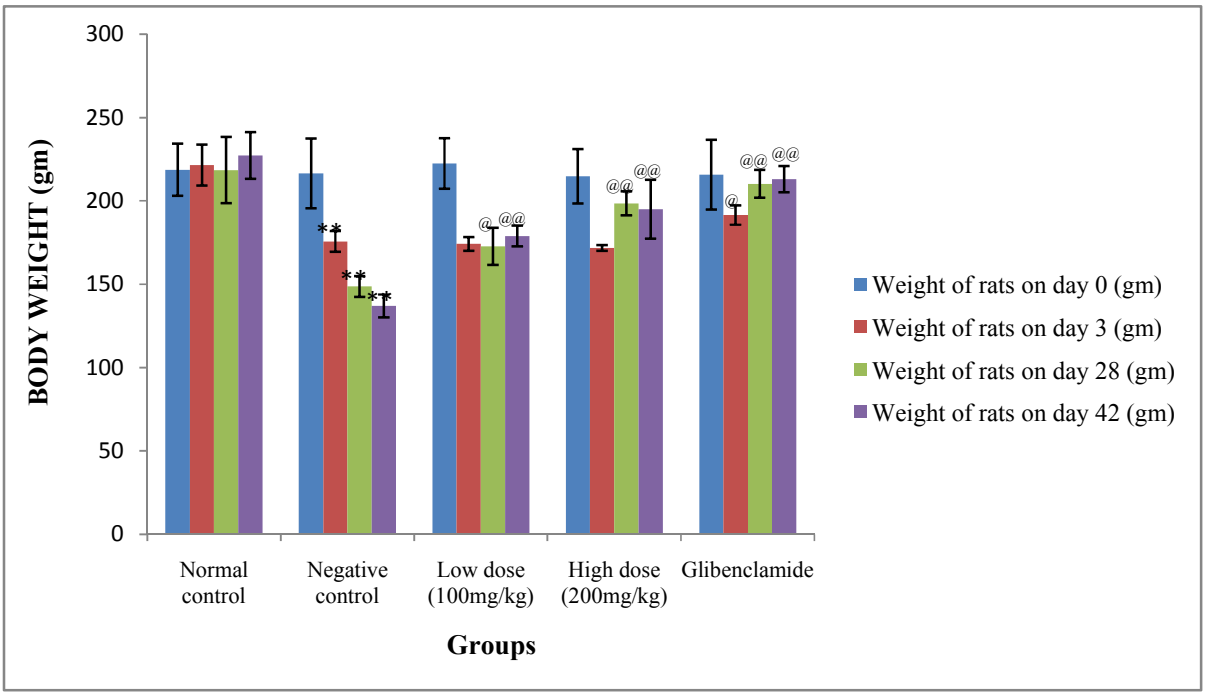

Fig. No. 2: Evaluation of body weight of rats on day 0, 3, 28 and 42.

Table No. 2 and Figure No. 2 shows the effect of *Euphorbia milii* leaves extract on body weight of streptozotozin induced diabetic rats, there was significant decrease ($p<0.01$) in the body weight in negative control group compared to normal control group of rats on day 3, 28 and 42. This decrease in the body weight confirms the loss of body weight in diabetes in the rats. After Drug treatment, there was significant improvement ($p<0.01$) in low dose group (100mg/kg), high dose group (200mg/kg) and Standard dose group compared to negative control groups on day 28 and 42.

Table No 3: Estimation of blood glucose level of rats on day 0, 3, 28 and 42.

Group	Glucose Level on day 0 (mg/dl)	Glucose Level on day 3 (mg/dl)	Glucose Level on day 28 (mg/dl)	Glucose Level on day 42 (mg/dl)
Normal control	100.14 ± 5.24	99.07 ± 2.75	101.54 ± 4.43	100.55 ± 2.27
Negative control	98.56 ± 5.02^{ns}	186.50 ± 4.41**	221.82 ± 4.41**	240.23 ± 6.99**
Low dose	102.63 ± 5.01^{ns}	189.87 ± 7.24^{ns}	189.6 ± 5.87$^{@@}$	179.09 ± 9.15$^{@@}$

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High dose	102.78 ± 3.62^{ns}	187.15 ± 5.56^{ns}	168.11 ± 7.86$^{@@}$	156.66 ± 9.32$^{@@}$
Standard dose	98.66 ± 4.32^{ns}	166.30 ± 3.21$^{@@}$	158.80 ± 9.14$^{@@}$	149.89 ± 10.31$^{@@}$

The result were expressed as Mean ± SD (n = 4)

^{ns} (*not significant)* = p>0.05, **p<0.01 when compared to normal control group of rats

^{ns} (*not significant)* = p>0.05, $^{@@}p$<0.01 when compared to negative control group of rats

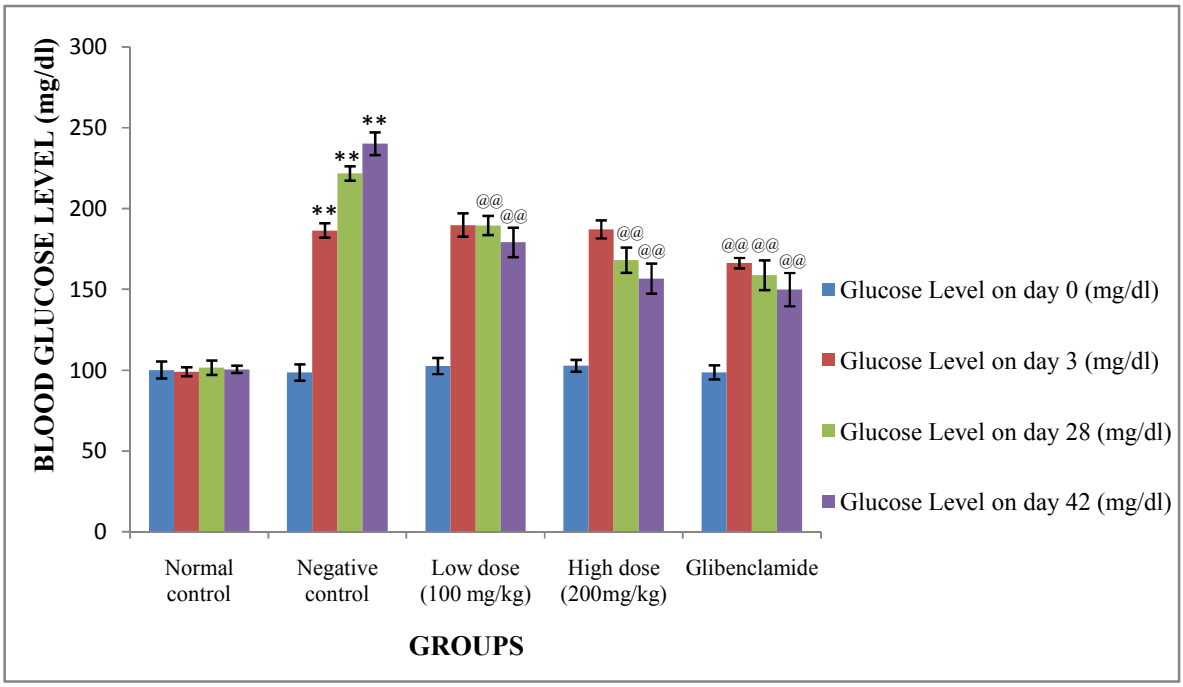

Fig. No. 3: Estimation of blood glucose level of rats on day 0, 3, 28 and 42.

Table No. 3 and Figure No. 3shows the effect of *Euphorbia milii* leaves extract on blood glucose levels of streptozotozin induced diabetic rats, There was significant increase (p<0.01) in the blood glucose levels in negative control group compared to normal control group of rats on day 3, 28 and 42. This increase in the Blood glucose levels confirms the diabetes in the rats. After drug treatment there was significant decrease (p>0.01) in the Blood glucose level in low dose group (100mg/kg), high dose group (200mg/kg) and Standard dose group compared to negative control groups on day 28 and 42.

3.3 Effect of MEEM on Thermal Hyperalgesia (Tail Flick Test):

Table No. 4: Tail Flick response of rats on day 0, 3, 28 and 42.

Group	Tail Flick Response on day 0 (sec)	Tail Flick Response on day 3 (sec)	Tail Flick Response on day 28 (sec)	Tail Flick Response on day 42 (sec)
Normal control	5.75 ± 0.08	5.61 ± 0.08	5.59 ± 0.13	5.61 ± 0.08
Negative control	5.78 ± 0.12^{ns}	4.60 ± 0.32**	3.58 ± 0.28**	3.01 ± 0.28**
Low dose	5.73 ± 0.09^{ns}	4.66 ± 0.21^{ns}	5.40 ± 0.27$^{@@}$	5.17 ± 0.11$^{@@}$
High dose	5.72 ± 0.12^{ns}	4.48 ± 0.14^{ns}	5.61 ± 0.07$^{@@}$	5.55 ± 0.10$^{@@}$
Glibenclamide	5.62 ± 0.08^{ns}	5.16 ± 0.23$^{@@}$	5.79 ± 0.15$^{@@}$	5.64 ± 0.18$^{@@}$

The result were expressed as Mean ± SD (n = 4)

^{ns} (*not significant)* = p>0.05, **p<0.01 when compared to normal control group of rats

^{ns} (*not significant)* = p>0.05, $^{@@}p$<0.01 when compared to negative control group of rats

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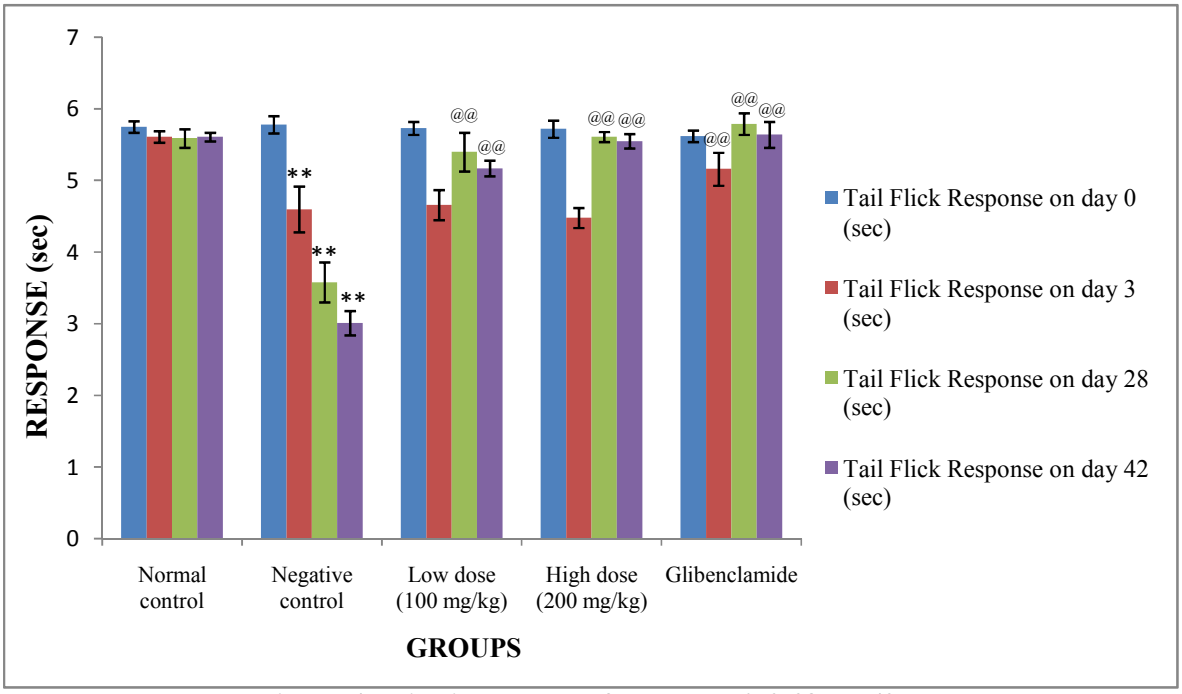

Fig. No. 4: Tail Flick response of rats on day 0, 3, 28 and 42.

Table No. 4 and Figure No. 4 reveals the effect of *Euphorbia milii* leaves extract on tail flick pain sensation effect of streptozotocin induced diabetic rats, There was significant decrease ($p<0.01$) in the analgesic effect of rats in negative control group compared to normal control group of rats on day 3, 28 and 42. This decrease in the analgesic effect confirms the hyperalgesia in rats. After drug treatment, there was Significant improvement ($p<0.01$) in tail flick response in low dose group (100mg/kg), high dose group (200mg/kg) and Standard dose group compared to negative control groups on day 28 and 42.

3.4 Effect of MEEM on Motor Coordination (Rota Rod Test):

Table No.5: Muscle co-ordination response of rats on rota rod apparatus on day 0, 3, 28 and 42.

Groups	On day 0 Mean Falling Time MFT (sec)	On day 3 Mean Falling Time MFT (sec)	On day 28 Mean Falling Time MFT (sec)	On day 42 Mean Falling Time MFT (sec)
Normal control	58.82 ± 3.74	53.62 ± 2.67	56.06 ± 2.63	59.86 ± 3.02
Negative control	55.12 ± 3.57^{ns}	$47.61 \pm 3.24^{*}$	$39.98 \pm 3.23^{**}$	$31.06 \pm 3.52^{**}$
Low dose	55.57 ± 4.00^{ns}	48.82 ± 3.45^{ns}	40.08 ± 2.15^{ns}	$39.35 \pm 2.26^{@@}$
High dose	60.48 ± 3.46^{ns}	48.79 ± 2.00^{ns}	39.35 ± 2.53^{ns}	$48.59 \pm 2.61^{@@}$
Glibenclamide	59.80 ± 3.70^{ns}	50.66 ± 2.16^{ns}	39.87 ± 1.24^{ns}	$57.33 \pm 2.51^{@@}$

The result were expressed as Mean ± SD (n = 4)

^{ns} (*not significant*) = $p>0.05$, $^{**}p<0.01$ when compared to normal control group of rats
^{ns} (*not significant*) = $p>0.05$, $^{@@}p<0.01$ when compared to negative control group of rats

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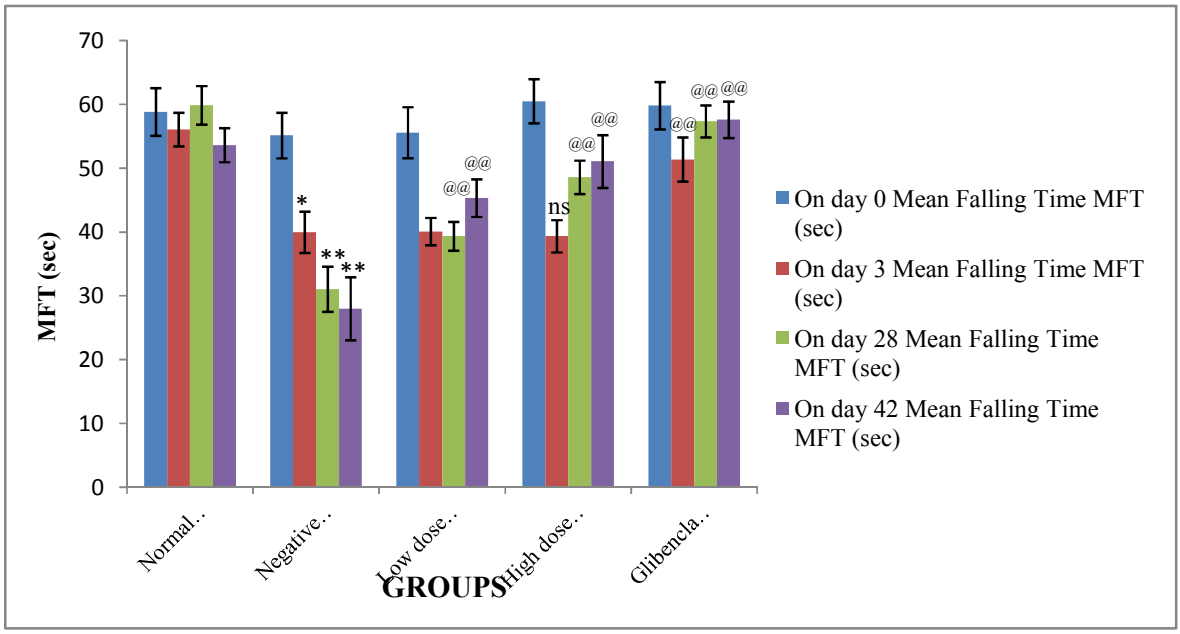

Fig, No. 5: Muscle co-ordination response of rats on rota rod apparatus on day 0, 3, 28 and 42.

Table No. 5 and Figure No. 5 reflect the effect of *Euphorbia milii* leaves extract on muscle strength of streptozotocin induced diabetic rats, There was significant decrease ($p<0.01$) in the muscle strength of rats in negative control group compared to normal control group of rats on day 3, 28 and 42. This decrease in the muscle coordination confirms Neuropathy, After drug treatment there was significant improvement ($p<0.01$) in the muscle Co-ordination in low dose group (100mg/kg), high dose group (200mg/kg) and Standard dose group compared to negative control groups on day 28 and 42.

IV. DISCUSSION

This study investigated the potential of methanolic extract of *Euphorbia milii* leaves (MEEM) to alleviate diabetic neuropathic pain in STZ-induced diabetic rats. The successful induction of diabetes was confirmed by sustained hyperglycemia and a significant decrease in body weight in the STZ-treated group. Treatment with both low (100 mg/kg) and high (200 mg/kg) doses of MEEM on day 28 and 42 demonstrated significant improvements in both thermal hyperalgesia and motor coordination deficits in diabetic rats. The increased tail flick latency suggests that MEEM possesses analgesic properties, potentially by modulating pain pathways or reducing nerve damage. The improved performance on the rota rod apparatus indicates a potential neuroprotective effect, possibly by enhancing nerve function and muscle strength. The high dose of MEEM exhibited comparable efficacy to the standard drug, glibenclamide, in both pain reduction and improvement of motor coordination.

The observed effects of MEEM could be attributed to the presence of various bioactive phytochemicals identified in the extract, including flavonoids, terpenoids, and phenolic compounds. Flavonoids and phenolic compounds are known for their potent antioxidant and anti-inflammatory properties. In diabetic neuropathy, hyperglycemia-induced oxidative stress and inflammation play a crucial role in nerve damage and the development of neuropathic pain. The ability of MEEM to reduce blood glucose levels, as observed in this study, may also contribute to its beneficial effects on diabetic neuropathy by mitigating the primary cause of nerve damage.

The analgesic effect of MEEM might be mediated by the modulation of pain signaling pathways. Some phytochemicals, such as flavonoids and terpenoids, have been shown to interact with neurotransmitter systems and ion channels involved in pain transmission. Furthermore, the potential neuroprotective effect of MEEM, leading to

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improved motor coordination, could be due to its ability to enhance nerve regeneration, improve nerve conduction velocity, or protect against further nerve degeneration.

V. CONCLUSION

The findings of this study demonstrate that the methanolic extract of *Euphorbia milii* leaves possesses significant potential in alleviating diabetic neuropathic pain and improving motor coordination deficits in STZ-induced diabetic rats. These effects are likely mediated by the combined action of its various phytochemical constituents, possibly through antioxidant, anti-inflammatory, and hypoglycemic mechanisms. Further studies are warranted to isolate and identify the specific bioactive compounds responsible for these effects and to elucidate their precise mechanisms of action. These findings provide a scientific basis for the traditional use of *Euphorbia milii* and suggest its potential as a source for developing novel therapeutic agents for managing diabetic neuropathy.

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