Evaluation of *Jatropha Integerrima* Leaves Extract in Diabetic Neuropathic Pain in Rats.

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***Abstract*:-**

Diabetic neuropathy is a prevalent complication of diabetes mellitus, leading to nerve damage, pain, sensory impairment, and reduced motor function. Current pharmacological treatments often exhibit limited efficacy and adverse side effects, highlighting the need for safer, plant-based alternatives. This study evaluates the therapeutic potential of *Jatropha integerrima* leaves extract in a streptozotocin-induced diabetic neuropathy model in rats. Methanolic extracts of the plant leaves underwent preliminary phytochemical screening, confirming the presence of bioactive compounds including alkaloids, flavonoids, glycosides, tannins, and steroids. Diabetes was induced in Sprague Dawley rats using streptozotocin (60 mg/kg), followed by confirmation of neuropathy through behavioral assessments such as the tail flick and rota rod tests. Treatment with *Jatropha integerrima* extract at 200 mg/kg and 400 mg/kg doses significantly reduced blood glucose levels, improved body weight, increased pain threshold, and enhanced motor coordination in diabetic rats. The higher dose (400 mg/kg) showed more pronounced therapeutic effects.

Keywords :- Jatropha Integerrima Leaves, Euphobiaceae, Diabetes Mellitus, Diabetic Neuropathy, Antioxidant.

I. INTRODUCTION

Diabetes is a condition where blood sugar levels are too high, either when fasting or after eating. Long-term high blood sugar (Diabetes Mellitus) can damage organs like the eyes, kidneys, nerves, heart, and blood vessels. The International Diabetes Federation (IDF) reports that diabetes is widespread. (Uazman Alam et al., 2014)

Diabetes Mellitus is a condition that affects how the body uses sugar, fat, and protein. It happens due to problems with insulin production. There are three main types: Insulin-Dependent Diabetes (IDDM), Non-Insulin-Dependent

Diabetes (NIDDM), and Gestational Diabetes. Common symptoms of untreated diabetes include weight loss, frequent urination, excessive thirst, and increased hunger. (Rohilla A. and Allis, 2012)

Diabetes mellitus is a group of conditions where high blood sugar happens because the body can't make or use insulin properly. This affects how the body handles sugar, fat, and protein. Low insulin levels or resistance to insulin can affect muscles, fat tissue, and the liver. Some people, especially those with type 2 diabetes, may not show symptoms at first. Others-especially children with no insulin-can have frequent urination, thirst, hunger, weight loss, and blurred vision. If not treated, diabetes can cause serious problems like coma or even death. (Kharrobi et al., 2015)

EPIDEMIOLOGY

Diabetes is becoming more common worldwide due to rising obesity and unhealthy lifestyles. In 2013, 382 million people had diabetes, and this number may reach 592 million by 2035. There are two main types of diabetes: type 1 and type 2, with type 2 making up over 85% of cases. Both types can cause serious health problems, such as eye, kidney, nerve, heart, and blood vessel damage. Diabetes also leads to early death, lower life expectancy, and high healthcare costs. (Nita Gandhi *et al*., 2010)

DIABETES COMPLICATIONS

- Eye problems – Can damage the eyes and lead to vision loss.
- Foot issues – Poor blood flow and nerve damage can harm the feet.
- Gum disease – High blood sugar helps bacteria grow in the mouth.
- Heart and stroke – Can damage blood vessels and nerves, increasing the risk.
- Kidney disease – Damaged kidney blood vessels may lead to kidney failure.
- Nerve damage – Affects the nerves and their blood supply.
- Skin issues – Poor circulation and blood vessel damage can cause skin problems. (Jessica L. Harding *et al*., 2019)

NEUROPATHY

Neuropathy means nerve damage that causes weakness, numbness, and pain-especially in the hands and feet. It can also affect digestion, blood pressure, and other body functions. Damaged nerves disrupt signals between the brain and body, leading to muscle weakness and tingling. Diabetic neuropathy is a common and expensive problem in both type 1 and type 2 diabetes. It usually shows up later in type 1, but can appear earlier in type 2. Diabetic patients may experience abnormal sensations, increased pain sensitivity, slow nerve signals, and worsening movement and sensation problems. (Dr. Abdiaziz Mohammad Shire, 2018)

PATHOPHYSIOLOGY

Even though scientists understand more about how diabetic complications develop, they still don't know why some people get painful nerve damage and others don't. Researchers are trying to understand the full picture of how neuropathy works, including why it causes pain and other symptoms. Interestingly, pain levels don't always match how severe the nerve damage is, and pain can happen even when nerves aren't visibly injured. (Anne K. Shrieber, 2015)

Important pathways involved in diabetic neuropathy (DN):

- Increased activity in the polyol pathway (a sugar-processing pathway)
- Stress from harmful oxygen and nitrogen molecules (oxidative and nitrosative stress)
- Changes in small blood vessels
- Abnormal nerve growth (called sprouting)
- Activation of brain immune cells (microglia)
- Increased sensitivity of the nervous system (central sensitization)
- Changes in the brain's ability to adapt (brain plasticity) (Anne K. Shrieber, 2015)

SIGN AND SYMPTOMS

- Tingling or burning sensation
- Numbness or reduced ability to feel pain or temperature
- Diarrhea and sexual dysfunction
- Muscle weakness
- Loss of bladder control
- Drooping of the face, mouth, or eyelids
- Vision problems (P. James, 2012)

CAUSES

- Good nutrition is important in managing diabetic peripheral neuropathy.
- Diabetic neuropathy can lead to serious complications, from heart rate changes to vision problems.
- Loss of feeling can delay noticing cuts or sores, leading to infections and possible amputation.
- People may lose feeling in their feet.
- Bladder and kidney infections can also develop.
- It's important for people with this condition to check their feet daily for injuries or sores. (P. James, 2012)

TREATMENT FOR DIABETIC NEUROPATHY

- If diabetic neuropathy causes sleep problems, TCAs (like amitriptyline) are often used first because they help improve sleep.
- Other TCAs like imipramine or nortriptyline may work better for some patients.
- Treatment usually starts with 10 mg at night, increasing slowly (up to 100-150 mg daily), to reduce side effects.

- It may take 3-4 weeks to feel the full effect.
- Metformin is another option, especially if symptoms continue. It can be combined with a low dose of TCA (10-25 mg), especially for sleep issues.
- Treatment is successful if it reduces pain or improves function, but full pain relief is rare.
- Patients should understand this early to set realistic expectations.
- Good blood sugar control, diet, and lifestyle changes are important to prevent and manage pain.
- Sudden changes in blood sugar should be avoided. (Carmallawint Cameron *et al*., 2015

HERBAL MEDICINE

It involve the medicinal uses of plant to treat diseases and enhance general health and well bing.

ADVANTAGES

- Can help reduce side effects
- Supports natural healing
- Improves overall health
- Can save money (D. M. Wood, 2004)

HERBAL MEDICINE USE IN DIABETIC NEUROPATHIC PAIN (DNP)

Herbal medicine is one of the oldest treatments used by people. Recently, more people prefer herbal remedies because they have fewer side effects and complications than synthetic drugs. As demand increases, research on using medicinal plants for treating painful neuropathy is also growing worldwide. (Fatemeh Forouzanfar *et al*., 2018)

II. EXPERIMENTAL WORK

Materials :-

Table 1:- Chemical and Reagent

Sr. No	Name of Chemical
1.	Petroleum Ether
2.	Ethanol
3.	Chloroform
4.	Streptozotocin
5.	Sulphuric Acid
6.	Sodium Nitropruside
7.	Glacial Acetic Acid
8.	Ferric Chloride
9.	Potassium Permanganate
10.	Lead Acetate
11.	Hydrochloride Acid
12.	Wagner Reagent
13.	Picric Acid

14.	Glucose Diagnostic Kit
15.	Pyrifine

Table 2 :- Instrument

Sr. No	Name of Instruments
1.	Analgesiometer
2.	Rota Rod Appratus

Animals :-

Healthy Sprague dawley male Rats approximately 8 weeks of age weighing about 200-250 gm were used for the study. The animal were house in polypropylene cages with wire mesh top and husk bedding and were maintained under standard condition and feed with standard pellet diet and water. The studies were carried out by following the guidelines given by com-mittee for the purpose of control and supervision of experiments on animals (CPCSEA), New Delhi (India). The study protocol was approved by The institutional Animal ethical committee

(IAEC 650/PO/Re/S-2002/2025/CCSEA/05).

Extraction :-

Leaves of Jatropha integerrima plant were collected and kept for shed drying for optimal period. After complete drying they were subjected for grinding in coarse powder by the mechanical means.

- The powdered leaves were kept for maceration in methanol medium for 72Hrs at room temperature and filtered.
- The filtrate was dried at 40° C
  Wt of empty pouch: 0.61 gm
  Wt of methanolic extract of *Jatropha integerrima* (32.12-0.61)
  = 31.51 gm
- Percentage Yield of methanolic extract of leaves of Jatropha integerrima
  % Yield = (30.68/3000) ×100
  % Yield = 1.050% w/w.

Phytochemical Screening :-

The obtained extract was screened for the different phytochemical constituents as

- TEST for STEROIDS (Brownlee M, 2001)
  Salkowski Test :- To 0.1 g of each extract, add 2 ml of chloroform ($CHCl_3$) and 2 ml of concentrated sulfuric acid (H_2SO_4). A reddish-brown color appears in both layers, indicating the presence of steroids.

- TEST for GLYCOSIDE (CARDIAC) (Dellon A. L, 2017)
  Keller-Killiani Test :- To 0.05 g of each extract, add 2 ml of glacial acetic acid and 1 ml of ferric chloride ($FeCl_3$) solution. Heat the mixture, then cool it. Carefully transfer it to a test tube containing 2 ml of concentrated sulfuric acid (H_2SO_4). A brown ring at the interface of the two layers indicates the presence of cardiac glycosides.

- TEST for TANINS (Brownlee M, 2001)
  Gelatin Test :- Add 1% gelatin solution with 10% NaCl to 2 ml of plant extract in a test tube. Mix well and let it stand. Formation of a white precipitate indicates the presence of tannins.

- TEST for FLAVONOIDS (Dellon A. L, 2017)
  Lead Acetate Test :- Add 5 ml of lead acetate solution to 0.1 g of each extract. A yellow precipitate indicates the presence of flavonoids.

- TEST for ALKALOIDS (Brownlee M, 2001)
  Mayer's Test :- Add a few drops of Mayer's reagent to 0.2 g of plant extract. A creamy precipitate indicates the presence of alkaloids.

Experimental design:-

The animals were divided into five groups, with 6 animals in each group as follow:

- Group-1 (Normal Control) = Animals were treated with normal saline solution
- Group-2 (Negative Control) = Diabetes was induced in rats using STZ (60 mg/kg i.p).
- Group-3 (Low Dose) = Diabetic rats were treated with 200 mg/kg of extract of J.I. leaves.
- Group-4 (High Dose) = Diabetic rats were treated with 400 mg/kg of extract of J.I. leaves.
- Group -5 (Standard) = Diabetic rats were treated with standard drug (Metformin 25 mg/kg).

Induction of Diabetic Neuropathy

Diabetes was induced by giving an intraperitoneal injection of STZ (60 mg/kg) to overnight-fasted animals. After three days, fasting blood glucose levels were measured using a glucose diagnostic kit (Ambica Diagnostics). Animals with glucose levels above 200 mg/dl were considered diabetic. (Aminique Sigaudo-Roussel *et al*., 2007) Diabetic neuropathy was confirmed 4 week of Induction of Diabetes by following models:

Checked by Neuropathy

A] Thermal Method

Tail Flick Method :-

The Tail Flick Test is used to measure pain response and the effectiveness of pain-relieving drugs. Heat is applied to the rat's tail, usually by focusing intense light or immersing it in hot water. When the rat flicks its tail, the reaction time is recorded. A cutoff time of 10 seconds is set to prevent injury. After 28 days of diabetes induction, rats in both the untreated (negative) and treated groups showed increased sensitivity to pain (hyperalgesia), confirming neuropathic pain. (Chakradhar Tripathi, 2016)

B] Mechanical Method

Rota Rod Method :-

The Rota Rod test assesses motor skills in rodents by placing them on a rotating rod. It measures how long they can stay on, helping evaluate balance, grip strength, endurance, and coordination. This test is commonly used to study the effects of experimental drugs or brain injuries. (S. Niknia, et al., 2019)

After 28 days, the animals were tested on a Rota Rod rotating at 25 rpm. The time each rat stayed on the rod was recorded. A shorter fall time compared to the control group indicated reduced muscle strength. (S. Niknia et al., 2019)

STATASTICAL ANALYSIS :-

The data are expressed as the mean I standard deviation (SD). Statistical analyses were performed utilizing InStat version 3 Software. To determine the significance were of difference between experimental groups, the student's t-test was applied. The levels of significance were denoted by p-values, with the significance threshold indicated as follows: $^{@}p<0.05$, *p<0.01, **p<0.001, $^{\#}P<0.001$ $^{@@}p > 0.05$ with each symbolizing increasing level of an Statistical significance.

III. RESULTS

Preliminary Phytochemical Screening of Extract

Table 3:- Result of phytochemical screening of hydro alcoholic extract of *Jatropha integerrima* leaves extract.

Sr. No	Plant Constituent	Test performed and Reagents	*Jatropha integerrima* Extract
1.	Test for Alkoloids	Mayer's Test	+
2.	Test for Carbohydrates	Benedict Test Fehling Test	+ -
3.	Test for Glycoside	Keller-Killiani Test	+
4.	Test for Protein	Biuret Test Lead Acetate	+ +
5.	Test for Tannins	Gelatin Test	+
6.	Test for Steroids	Salkowski Test	+
7.	Test for Flavonoids	Lead Acetate Test	+

EVALUATION OF DIABETIC PARAMETERS IN RATS

1] BODY WEIGHT

Table 4:- Evaluation of Body Weight of Rats on 0, 3rd, 28th & 42nd day

Groups	Weight of rat on day 0 (gm)	Weight of rat on day 3rd (gm)	Weight of rat on day 28th (gm)	Weight of rat on day 42nd (gm)
Control	224±4.54	244±7.62	247±11.83	245 ±12.67
Negative Control	220 ± 4.29	213±6.43$^{@}$	196 ± 11.59**	177±12.17**
J.I. (200mg/kg)	234 ± 4.49	213±6.67^{ns}	216 ± 11.63*	222 ±12.60*
J.I. (400mg/kg)	228 ± 4.41	218 ±6.52^{ns}	219 ± 11.34*	208 ±12.26*
Metformin (25mg/kg)	226±4.38	214±6.31^{ns}	226±11.48$^{\#}$	219 ±12.42$^{\#}$

$^{@}$P<0.05, **p <0.001 when compared to Control group of rats.

^{ns}p>0.05, *p<0.01, $^{\#}$p<0.00l when compared to Negative Control group of rats.

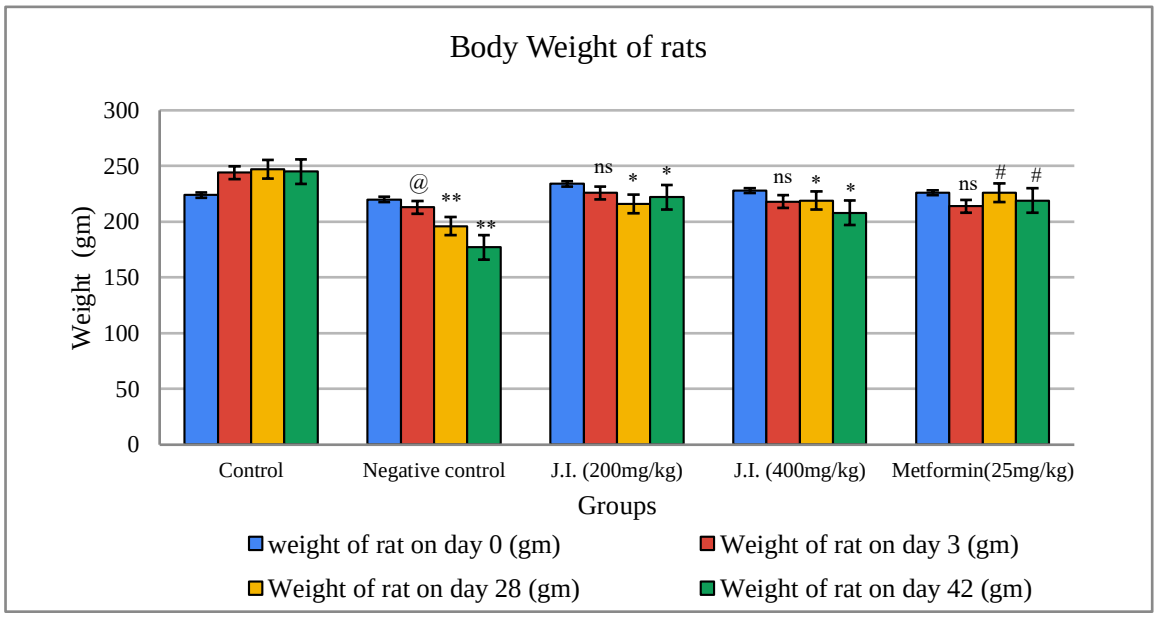

Fig 1 :- Evaluation of Body Weight of Rats on 0, 3rd, 28th& 42nd day

The effect of STZ on body weight of the rats on day 0, 3rd, 28th and 42nd. There was significant decrease ($p < 0.01$) in the body weight in groups of rats when compared to control group of rats on day 3rd, 28th and 42nd. This decrease in the body weight is due to diabetes in the rats. After confirmation of DN, rats were treated with methonolic extract of *Jatropha integerrima* leaves for two weeks. After drug treatment, there was significant improvement in ($p < 0.01$) in the body weight in *Jatropha integerrima* leaves extract (400mg/kg). *Jatropha integerrima* leaves extract (200mg/kg) and Metformin (25mg/kg) treated group when compared to Negative control Group.

2] EVALUATION OF BLOOD GLUCOSE LEVEL

Table 5:- Evaluation of Blood Glucose Level of Rats on 0, 3rd, 28th & 42nd day

Groups	Blood Glucose Level of Rat on day 0 (mg/dl)	Blood Glucose Level of Rat on day 3rd (mg/dl)	Blood Glucose Level of Rat on day 28th (mg/dl)	Blood Glucose Level of Rat on day 42nd (mg/dl
Control	103.23±3.21	105.43 ±21.24	118.45±27.43	108.37±21.32
Negative Control	110.43 ±3.42	172.66±21.86*	218.8±27.67**	233.58±23.23**
J. I. (200mg/kg)	108.67±3.28	186.75±22.18ns	226.36±28.54ns	183.73±2248@
J. I. (400mg/kg)	117.54 ±3.53	198.66±22.33ns	237.27±29.78ns	172.32±22.04@
Metformin (25mg/kg)	112.29 ±3.45	207.45±22.35ns	248.33±29.27ns	168.69±21.92#

*p<0.01, **p <0.001 when compared to Control group of rats.

nsp<0.05, #p<0.001, @p<0.05 when compared to Negative Control group of rats.

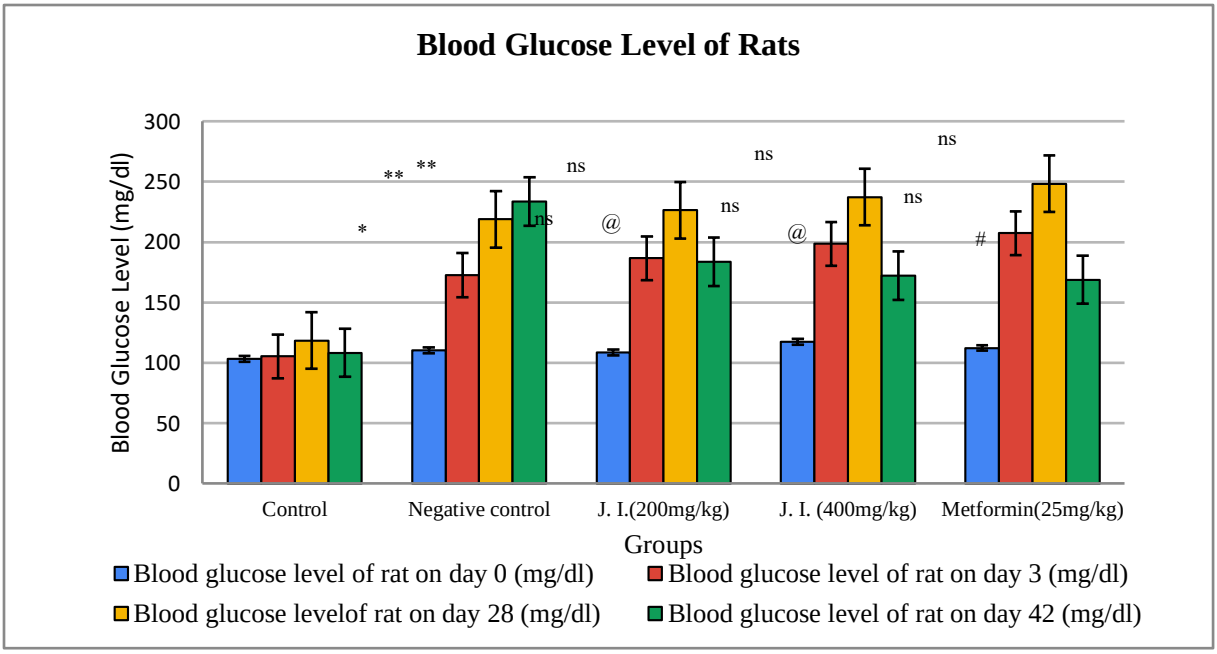

Fig 2 :- Evaluation of Blood Glucose Level of Rats on 0, 3rd, 28th& 42nd day

The effect of STZ on Blood Glucose Level of the rats on day 0, 3rd , 28th and 42nd. There was significant decrease ($p < 0.01$) in the Blood Glucose Level in groups of rats when compared to control group of rats on day 3rd , 28th and 42nd. This decrease in the Blood Glucose Level is due to diabetes in the rats. After confirmation of DN, rats were treated with methanolic extract of *Jatropha integerrima* leaves for two weeks. After drug treatment, there was significant decrease in ($p < 0.01$) in the Blood Glucose Level in *Jatropha integerrima* leaves extract (400mg/kg) *Jatropha integerrima* leaves extract (200mg/kg) and Metformin (25mg/kg) treated group when compared to Negative control Group

3] TAIL FLICK METHOD

Table 6 :- Tail flick Response of rats on 0, 3rd, 28th& 42nd day

Group	Tail flick response of rat on day 0 (in sec)	Tail flick response of rat on day 3 (in sec)	Tail flick response of rat on day 28 (in sec)	Tail flick response of rat on day 42 (in sec)
Control	5.48 ± 0.13	5.34±0.12	5.67 ± 0.6	5.18 ± 0.64
Negative control	5.83 ± 0.15	5.27 ± 0.11^{ns}	4.32 ± 0.59**	3.56 ± 0.58**
J.I. (200 mg / kg)	5.76 ± 0.14	$5.17 \pm 0.10^{@@}$	$4.98 \pm 0.63^{@}$	$5.59 \pm 0.66^{@}$
J.I. (400mg / kg)	5.94 ± 0.15	$5.45 \pm 0.13^{@@}$	$4.13 \pm 0.54^{@@}$	$5.48 \pm 0.65^{\#}$
Metformin (25mg / kg)	5.89 ± 0.15	$5.44 \pm 0.13^{@@}$	$4.78 \pm 0.61^{@}$	$5.17 \pm 0.64^{\#}$

The results were expressed as Mean ±SD (n=6)

$^{ns}p > 0.05$, **$p < 0.001$, when compared to Control group of rats.

$^{@@}p > 0.05$, $^{@}p < 0.05$, $^{\#}p < 0.001$ when compared to Negative Control group of rats.

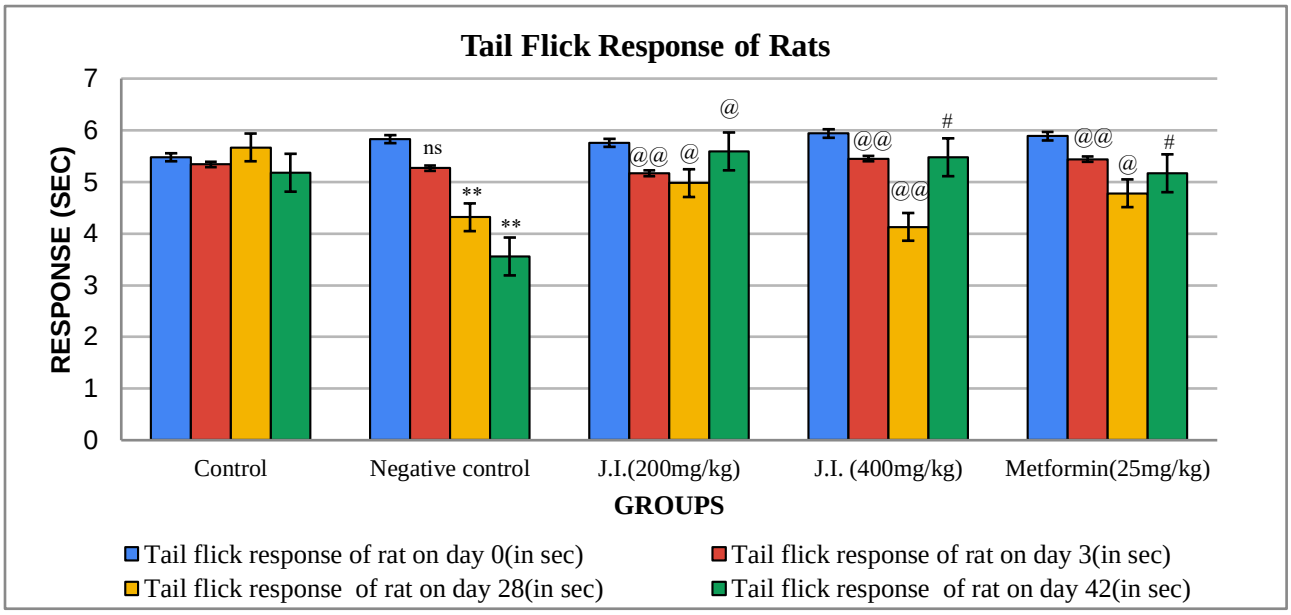

Fig 3 :- Tail Flick Response of Rats on 0, 3rd, 28th& 42nd day

The effect of STZ on tail flick pain sensation effect of the rats on 0, 3rd ,28th& 42nd day of STZ induction. There was significant decrease ($p<0.01$) in the analgesic effect of rats compared to control group of rats. This decrease in the analgesic effect confirms the hyperalgesia in the rats. After the conformation of Diabetic Neuropathy rats were treated with methanolic extract of *Jatropha integerrima* leaves extract for two weeks. After drug treatment, there was significant improvement the Tail flick response in STZ + *Jatropha integerrima* leaves extract (400 mg/kg) and STZ + *Jatropha integerrima* leaves extract ($p< 0.01$) (200 mg kg) and Metformin (25mg/kg) treated group compared to Negative control Group.

4] ROTA ROD METHOD

Table 7 :- Muscles Co-ordination response on Rota Rod on 0, 3rd, 28th& 42nd day

Group	Mean falling time of rat on day 0 (in sec)	Mean falling time of rat on day 3 (in sec)	Mean falling time of rat on day 28 (in sec)	Mean falling time of rat on day 42 (in sec)
Control	57.54 ± 2.09	64.62 ± 3.45	61.32 ± 6.44	59.77 ± 6.56
Negative control	56.62 ± 2.12	48.27 ± 3.61**	33.87 ± 5.27**	26.68 ± 6.21**
J.I. (200mg / kg)	67.32 ± 2.51	53.55 ± 3.63@	47.61 ± 5.57*	56.43 ± 6.49#
J.I. (400mg / kg)	64.17 ± 2.45	58.68 ± 3.76#	46.84 ± 5.42*	60.23 ± 6.62#
Metformin (25mg / kg)	63.43 ± 2.32	54.76 ± 3.78*	47.43 ± 5.32*	58.39 ± 6.54#

The results were expressed as Mean ±SD (n=6)

**p < 0.001 when compared to Control group of rats.

@p < 0.05, *p < 0.01, #p < 0.001 when compared to Negative Control group of rats.

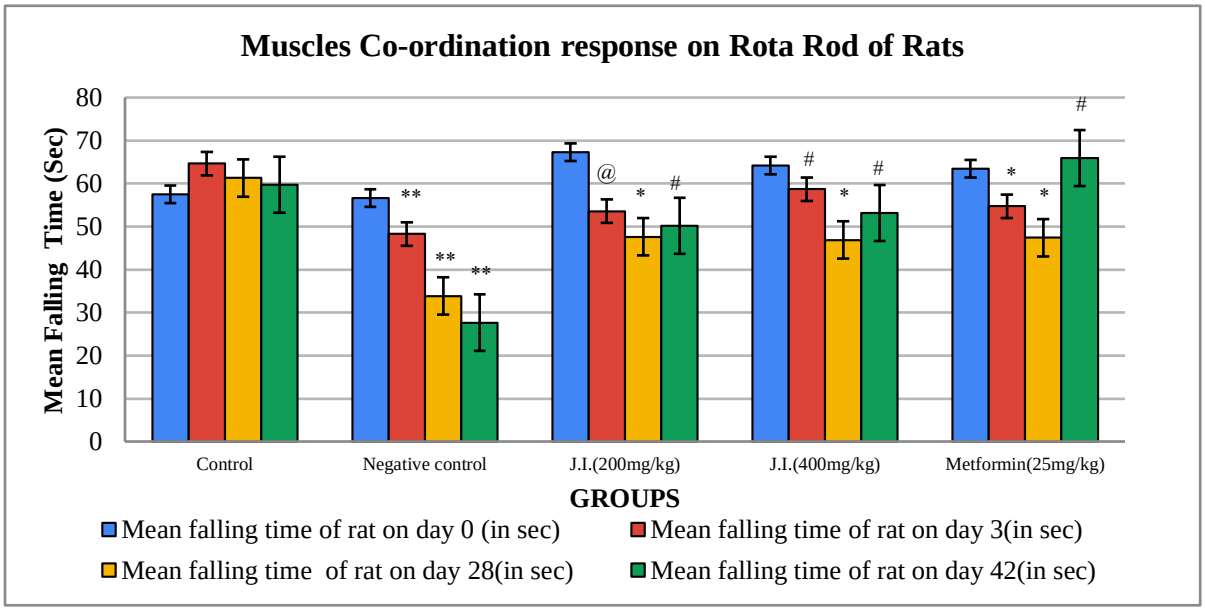

Fig 4 :- Muscles Co-ordination response on Rota Rod on 0, 3rd, 28th& 42nd day

The effect of STZ on muscle strength of the rats on 3rd, 28th& 42nd day of STZ induction. There was significant decrease ($p < 0.01$) in the muscle strength of rats compared to control group of rats. This decrease in the muscle coordination confirms the loss of muscle strength in the rats. After the conformation of Diabetic Neuropathy, rats were treated with methanolic extract of for two weeks. After drug treatment there was significant improvement (0.01) in the muscle coordination in STZ + *Jatropha integerrima* leaves extract (400 mg/kg) and STZ+ *Jatropha integerrima* leaves extract (200 mg/kg) and Metformin (25 mg/kg)treated group compared to Negative control Group.

IV. DISCUSSION

This study aimed to find out if an extract from *Jatropha integerrina* leaves could help relieve diabetic nerve pain in rats. The researchers tested whether natural compounds in the extract could reduce pain-related behaviors and symptoms caused by diabetes. (Dubinskt *et. al*., 2010)

All experiments were done in a controlled lab setting, following ethical rules for animal research. Sprague Dawley rats were used and allowed to get used to the lab environment before the study began. (Chaudhary *et, al*., 2018)

The study was done in several steps:

1. **Causing Diabetes:**

   Rats were given a single injection of streptozotocin (STZ) at 60 mg per kg of body weight to induce diabetes. After 72 hours, their blood sugar levels were checked. Rats with fasting glucose levels over 250 mg/dl were considered diabetic and included in the study. (Akram T *et, al*., 2015)

2. **Confirming Neuropathic Pain:**

   Diabetic nerve pain was allowed to develop over 3–4 weeks. During this time, behavior tests were done to check for signs of pain. Rats that showed clear pain symptoms compared to healthy ones were chosen for treatment. (Liux & Zhang, 2018)

3. **Treatment Phase:**

   The diabetic rats were split into groups: one with no treatment (control), one given standard medicine like metformin, and others given different doses of *Jatropha integerrina* leaves extract. The extract was given by mouth for 21 days. The doses were chosen based on earlier safety and plant compound tests. (Pandhare R. *et, al*., 2012)

4. **Pain Relief (Analgesic) Assessment:**

   During the treatment, behavior tests were done regularly to check changes in pain sensitivity. Rats treated with the extract showed clear pain relief in the Tail Flick Test and less sensitivity in the Rota Rod Test, indicating pain-reducing effects. (Kumar *et, al*., 2018)

- Diabetic neuropathy is associated with oxidative stress due to excess glucose metabolism, leading to the production of reactive oxygen species (ROS).
- Flavonoids scavenge free radicals, reduce oxidative damage, and improve mitochondrial function in neurons.

SCIENTIFIC IMPORTANCE:

This study supports the use of plant-based medicine to help manage diabetes-related problems. The *Jatropha integerrina* leaves extract clearly reduced nerve pain in diabetic rats, showing it could be a useful alternative or add-on treatment for diabetic neuropathy. However, more research is needed to understand how it works.

FUTURE RESEARCH SHOULD FOCUS ON:

- Finding and identifying the active compounds responsible for the effects
- Studying how the extract affects nerve structure, inflammation, and oxidative stress
- Testing the extract's safety over longer periods

- Understanding how the extract is absorbed, processed, and works in the body
- Exploring how it works when used with standard drugs like metformin.

V. CONCLUSION

This study shows that *Jatropha integerrima* leaves extract can help treat nerve damage caused by diabetes. The methanolic extract lowered blood sugar levels and improved body weight in diabetic rats. It also improved muscle coordination and reduced pain more effectively than the untreated group.

Overall, the extract appears helpful for managing diabetic neuropathy. Future research should focus on developing a herbal treatment plan using this extract with minimal side effects.

VI. ACKNOWLEDGEMENT

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