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EFFECTS OF N-BUTANOLIC FRACTION OF METHANOLIC EXTRACT OF *CUCUMIS SATIVUS* IN STZ INDUCED HYPERGLYCEMIA AND DIABETIC NEUROPATHY

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Abstract: A collection of metabolic disorders known as diabetes mellitus have become widespread, with a global incidence of 5% in the general population.one of the most challenging types Nerve damage brought on by diabetic neuropathy (nerve disease) primarily impacts the legs and feet. A substance called streptozotocin has antibacterial, cancer-causing, and diabetogenic characteristics. It is a broad-spectrum antibiotic that is produced by the streptomyces griseus metabolite. Toxic levels of STZ are found in pancreatic cells. The binding to cell membrane glucoreceptors is the mechanism of action. Although STZ contains a glucose molecule, the cell membrane's glucose receptors still recognise it as a glucose molecule, which leads to the inhibition of insulin secretion[67].For the purpose of causing diabetes, we administered STZ in several doses (40 mg/kg, over the course of five days). According to observations, the study's rats had their diabetes successfully created. It has been proven that M. cymbalaria's crude saponins have antidiabetic and antihyperlipidemic properties. According to reports, the saponins in momordica charantia, including charantin, momordicine, an insulin-like steroidal saponin, triterpene saponins, etc., are what provide the plant its antidiabetic properties. Animal models for thermal hyperalgesia (Tail Flick, Hot plate) and motor incoordination (Rota rod test) were used to study the diabetic neuropathy. It is intended that these models serve as behavioural indicators for diabetic neuropathy. After three weeks, the diabetic control group begins to show signs of neuropathy, but the treated group has significantly improved; as a result, BFCS lessens diabetic neuropathy.

Keywords: STZ, Diabetic neuropathy, hyperglycaemia, *Cucumis sativus*, Diabetes mellitus

1. INTRODUCTION

A group of metabolic disorders known as diabetes mellitus include hyperglycemia (high blood glucose levels), glycosuria, hyperlipidaemia, polyuria, polyphagia, polydipsia, negative nitrogen balance, and occasionally ketonemia. Hyperglycemia is caused by problems with insulin secretion, insulin response, or both. The development and progression of diabetes mellitus' problems may be significantly influenced by free radicals.[2] Multiple metabolic abnormalities and oxidative stress, particularly an increased susceptibility to lipid peroxidation, are produced by chronic hyperglycemia and contribute to the evolution of diabetes symptoms.[3] It now has a 5% global incidence in the general population, making it an epidemic. Every year, there are more people diagnosed with diabetes, which now claims more lives than AIDS. Until this point, India had 40.8 million diabetes patients compared to 40 million HIV patients worldwide. Diabetes currently affects up to 171 million people worldwide, and by 2030, this number is expected to have more than doubled. Diabetes-related issues are thought to be a contributing factor in close to 3.2 million annual deaths, or 6 deaths every minute. [4]
4.6 million People die from diabetes worldwide each year. According to research firm IMS Health, the $35 billion in global sales of diabetes medications last year might increase to $48 billion by 2015 due to increased prevalence and treatment, particularly in nations like China, India, Mexico, and Brazil. Asia is experiencing a faster growth of diabetics than the rest of the world as a whole. According to IDF estimates for 2010, six Asian nations—United Arab Emirates (18.7%), Saudi Arabia (16.8%), Bahrain (15.4%), Kuwait (14.6%), Oman (13.4%), and Malaysia (11.6%)—are among the top 10 nations in the world for diabetes prevalence. India (50.8 million people), China (43.2 million), Pakistan (7.1 million), Japan (7.1 million), and Indonesia (7 million) are the top five Asian nations by population. In 2030, Bangladesh is anticipated to surpass Japan and take the eighth position. In adults over 20 years old, the total prevalence rates of pre-diabetes and diabetes [including impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)] were 9.7 and 15.5 percent, respectively. The

number of diabetics was estimated to be 92.4 million adults at age 20 or older, and 148.2 million adults would have pre-diabetes [5].

1.1 Diabetic Neuropathy

A group of nerve illnesses known as diabetic neuropathies are brought on by diabetes. Diabetes patients run the risk of developing nerve damage throughout their bodies over time. Nerve injury can occur in people who show no symptoms. Some people may experience pain, tingling, or numbness, as well as a loss of feeling in their hands, arms, feet, and legs. Every organ system, including the heart, the digestive system, and the sex organs, is susceptible to nerve issues [6].

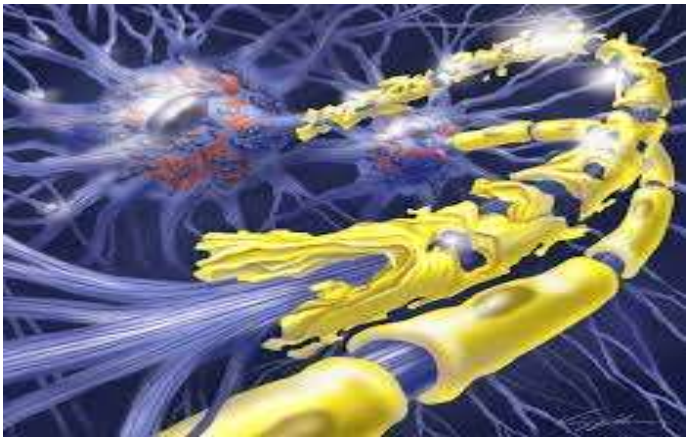

Fig No. 1 : Damaged myelinated nerve fiber[4]

Axonal degeneration, paranodal demyelination, the loss of myelinated nerve fibres, endoneurial ischemia damage, and reduced nerve conduction velocity are all related with diabetic neuropathy in human subjects[7].

1.2 Experimental Models of Diabetes Mellitus

1.2.1. Chemical induced diabetes

Streptozotocin(STZ) and alloxan-induced experimental diabetes are two examples of chemically induced diabetic models. Alloxan is a metabolite of uric acid and an anti-cancer drug. Alloxan prevents the release of insulin caused by glucose and, in large dosages, causes necrosis of cells. Alloxan also works by inhibiting the mitochondrial transport chain system, which results in an increase in intracellular pH and cell death. [08]

1.2.2 Streptozotocin Induced Diabetes

A substance called streptozotocin has antibacterial, cancer-causing, and diabetogenic characteristics. It is a broad-spectrum antibiotic that is produced by the streptomyces griseus metabolite. Toxic levels of STZ are found in pancreatic cells. The binding to cell membrane glucoreceptors is the mechanism of action. Although STZ contains a glucose molecule, the cell membrane's glucose receptors still recognise it as a glucose molecule, which leads to the inhibition of insulin secretion[10].

1.2.3 Brosius.Low dose streptozotocin induced protocol

Members of the AMDCC employ this procedure to cause diabetes in several of the group's produced animal models. This induction procedure is utilised to create a type I diabetes-like condition [68]. Combining herbal remedies with allopathic medications is a common therapeutic treatment. The majority of doctors did not record any complications; however the most frequent side effects associated with PHFs (Poly-herbal formulations) were nausea, vomiting, and gastrointestinal issues. Ayurvedic medicines are typically used because of their low toxicity[11]. The hypoglycemic effects of fruits from the Cucurbitaceae family, including Citrullus lanatus (sweet melon), Cucumis sativus (cucumber), Lagenaria siceraria (white pumpkin), Luffa acutangula (ridge gourd), Benincasa hispida (ash gourd), and Cucarbita maxima (pumpkin), on rats with alloxan-induced diabetes have been investigated. Cucurbitacins are so bitter that most people would avoid eating plants that contain them because of their intense bitterness. All sections of cucurbitaceous plants meant for food use are now typically free of cucurbitacins thanks to the original selection of non-bitter plants for food use by our ancestors and later by plant breeders. Andeweg and De Bruyn (1959) found one American variety of cucumber, Improved Long Green, after searching approximately 15,000 cucumber plants for non-bitterness of seedlings.[12]

With additional methods being used to enhance glycemic control through therapy, research has shown that diet plays a critical role in the prevention of chronic diseases like diabetes, making the goal of food conservation for people even more significant For the treatment and prevention of diabetes and its associated problems, it is crucial to pay special attention to functional food ingredients [13].

2. MATERIAL AND METHODS

2.1 Material: Collection of plant material:

Cucumber fruits were purchased from shahganj market Aurangabad.

2.2 Chemicals and drugs

Sr No.	Chemicals & drugs	Manufacturer
1	Petroleum ether	Himedia laboratories Ltd. Mumbai
2	Sodium chloride	Merck Specialities Pvt. Ltd. Mumbai
3	Sodium citrate	Himedia laboratories Ltd. Mumbai
4	Ethanol	Himedia laboratories Ltd. Mumbai
5	Methanol	Finar chemical Ltd. Ahmdabad
6	Streptozotocin	Spectrochem Pvt. Ltd. Mumbai
7	Metformin	Franco-Indian,pharmaceuticals, Mumbai
8	Ethyl acetate	Lobal chemie. Mumbai
9	N-butanol	Fisher Scientific India Pvt. Ltd. Mumbai

Table No. 1 : List of chemicals with respective manufacturer

Animals MaleWistar rat weighing between (180-200g) respectively were used. They were maintained at temperature of 25 ± 2˚C and relative humidity of 45 to 55% and under standard environmental conditions (12 h. light /12 h. dark cycles). The animals had free access to food (Pranav Agro Industries Ltd., Sangli, India) and water. All the experiments were carried out between 9 to 18 hrs. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Y.B. Chavan College of Pharmacy Aurangabad. (Approval number- CPCSEA/IAEC/P'cology- 40/2014-15/91

2.3. Extraction of Cucumber:

Sliced cucumber (Cucumis sativus) was acquired at a nearby market. The slices were dried completely before being pulverised into a coarse powder. (500g) of cucumber powder was weighed. Soxhlet extraction was used to create an extract. Using a Soxhlet extractor, petroleum ether was used to extract the dried powdered cucumber for 24 hours, followed by methanol for 48 hours. The extracts were concentrated at 60°C under reduced pressure, and the leftover extract was freeze-dried to produce a dark brownish residue. It was discovered that the extraction technique produced a yield of 1.81% w/w. Cucumis sativus's n- butanolic fraction was submitted to preliminary phytochemical screening [14, 15, 16].

2.4 Preparation of Drug solution:

2.4.1. Preparation of STZ solution:

Streptozotocin was always freshly produced for usage within 30 minutes and dissolved in cold 0.01 M citrate buffer with a pH of 4.5. STZ injections (40 mg/kg for 5 days straight) were administered intraperitoneally, and the doses were calculated based on the animals' body weights. From the day of the STZ injection, the blood glucose level was checked once a week [17].

2.4.2. Preliminary phytochemical evaluation of *Cucumis sativus* extract

Preliminary studies including Test for alkaloids such as Hager's test, Mayer's test, Dragendoff's test, Wagner's test and test for saponins such as; Froth Test, Test for tannin such as Ferric chloride test. Test for Glycosides such as Libeberman Buchard tests has carried out.{19,20,21,22]

Acute toxicity study toxicity study was done according to OECD guidelines 425

2.4.3. Induction of Experiental Diabetes

STZ was repeatedly injected into overnight-fasted rats for five days in a row at a dose of 40 mg/kg body weight. After the solution had dissolved in sodium citrate buffer pH 4.5, it was injected intraperitoneally (i.p.) within five minutes.As a vehicle control, distilled water was injected into the group A rat. To treat the drug-induced hypoglycemia, a 5% glucose solution was made available to the animals. At the time of the onset of diabetes, estimates of fasting blood glucose (FBG) and postprandial glucose (PPG) were made. These measurements were repeated until stable hyperglycemia was reached.

The rats with mild diabetes who had glycosuria and hyperglycemia (Blood glucose level of 300 mg/dl) after the week for the development of diabetes were included in the study as stable hyperglycemic animals. The medication therapy followed Table No. 4's instructions.2 the rat belonging to Group C were treated with an oral dose of metformin , Group D with n-butanolic fraction of cucumis sativus (50 mg/kg) , Group E with n-butanolic fraction of Cucumis sativus (25 mg/kg), Group F with n-butanolic fraction of Cucumi sativus (50 mg/kg) and Group G with n-butanolic fraction of Cucumis sativus (25 mg/kg) once every day for 21 consecutive days, while Group A and Group B rat received only distilled water (as vehicle control).

2.4.4. Assessment of antidiabetic activity

The animals were randomly divided into following groups:

Groups	Treatment	Dose
A	Normal Control	Distilled water
B	Diabetic Control	Distilled water
C	Diabetic + Metformin	120 mg/kg
D	Diabetic + N-butanol fraction of *Cucumis sativus*	10 mg/kg
E	Diabetic + N-butanol fraction of *Cucumis sativus*	25 mg/kg
F	Diabetic + N-butanol fraction of *Cucumis sativus*	50 mg/kg
G	Non-Diabetic + N-butanol fraction of *Cucumis sativus*	25 mg/kg

Table No. 2: Group and Treatment

2.4.5 Diabetic Neuropathy:

Within three days of receiving a streptozotocin injection, rats may have hyperalgesia and other clinical indications of diabetes. Within 7 to 15 days of receiving a streptozotocin injection, rats may have persistent mechanical allodynia and hyperalgesia. Different neuropathy markers were assessed in rats following the treatment period.[23,24,25,26]

Thermal sensitivity

Tail flick technique

Hot Plate technique

Groups	Treatment	Dose
A	Normal Control	Distilled water
B	Diabetic Control	Distilled water
C	Diabetic + Gabapentin	100 mg/kg
D	Diabetic + N-butanol fraction of *Cucumis sativus*	10 mg/kg
E	Diabetic + N-butanol fraction of *Cucumis sativus*	25 mg/kg
F	Diabetic + N-butanol fraction of Cucumis sativus	50 mg/kg
G	Non-Diabetic + N-butanol fraction of *Cucumis sativus*	25 mg/kg

Table No 3: Group and Treatment

3. RESULT

3.1. Preliminary Photochemical Evaluation

Sr No.	Photochemical Test	Inference
1	Test for Alkaloids Hagers Test	+
2	Test for Glycosides Libeberman Buchard test	+
3	Test for tannin Ferric chloride Test	-
4	Test for Triterpenoids	+
5	Test for Saponin Froth Test	+
6	Test for Phytosterol Lieberman Buchard test	-
7	Test for Flavonoids Lead acetate test	+

(- indicates absence and + indicate preesnce of phytoconstituents)

Table No 4: Preliminary Phytochemical Evaluation

The preliminary phytochemical investigation of n-butanol fraction of *cucumis sativus* revealed the presence of alkaloid, glycoside, triterpenoid, saponin and flaonoid.

3.2 Acute toxicity study:

According to the permitted range specified by OECD recommendations No. 425, animals treated with Cucumis sativus extract n- butanol fraction (BFCS) were free of any toxicity, and no mortality was discovered up to 2000 mg/kg. Therefore, the dosages of 10, 25, and 50 mg/kg were chosen for the investigation.

Effect of *Cucumis sativus* n-butanol fraction on Blood Glucose of Diabetic rat.

Group	Treatment
A	Normal Control
B	Diabetic Control
C	Diabetic + Metformin
D	Diabetic + N-butanol fraction of *Cucumis sativus*
E	Diabetic + N-butanol fraction of *Cucumis sativus*
F	Diabetic + N-butanol fraction of *Cucumis sativus*
G	Non-Diabetic + N-butanol fraction of *Cucumis sativus*

Table No. 5: Experimental Design for Diabetes

Group	**Fasting Blood Glucose Level (mg/dl)**	
	Initial	**3rd week**
A	97±2.950	99.8±1.463
B	540.2±25.56	572±10.32**
C	560.4±11.67	110.2±3.056**
D	578.8±18.95	151.6±8.358**
E	551.2±15.25	130±6.481**
F	518.2±16.85	147.8±15.30**

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G	121.2±5.851	111.2±1.356

Table No.6: Effect of *Cucumis sativus* n-butanol fraction on fasting Blood Glucose

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test.**p<0.01 vs Diabetic Control.

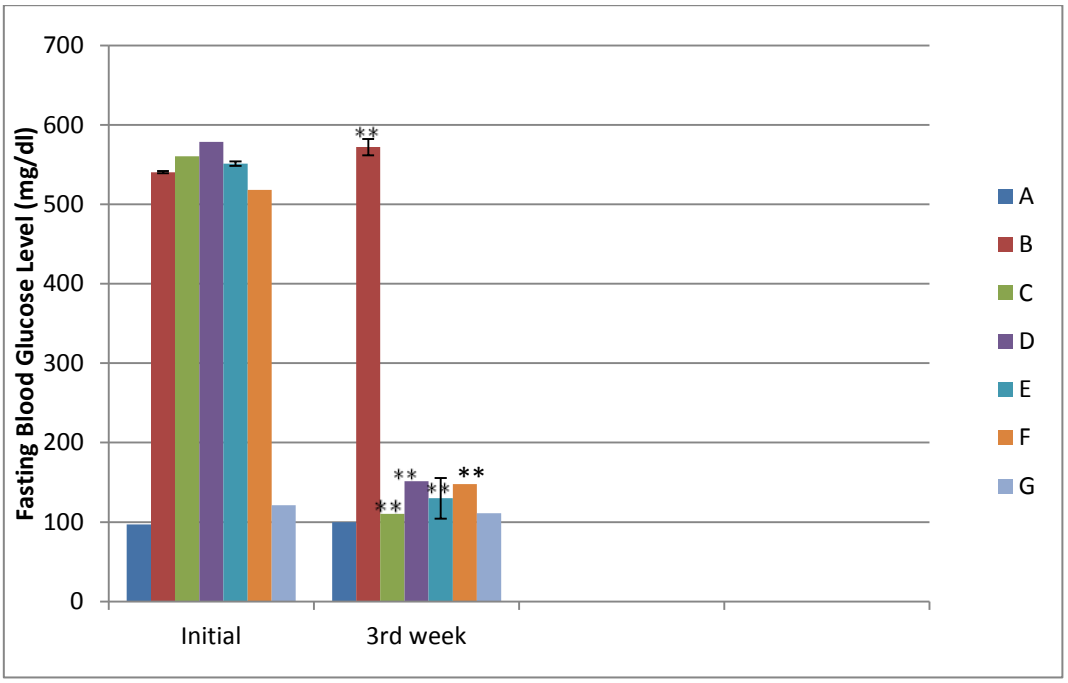

Fig No.2: Effect of *Cucumis sativus* on fasting Blood Glucose

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test.**p<0.01 vs Diabetic Control.

Body Weight:

Group	Body Weight **(mg/kg)**		
	Initial	**3rd week**	**Difference**
A	196.8±3.262	197.8±3.734**	1±3.209
B	231.2±7.838	138±3.937	-93.2±4.620
C	152.2±11.63**	135.8±9.557	-16.4±2.159
D	232.8±1.463	215.2±10.55**	-17.6±9.770
E	175.8±20.05*	147.2±11.03	-28.4±11.03
F	269.4±24.20	202±19.35**	-67.4±8.501
G	212±11.10	215±9.844**	3±9.171

Table No.7 Effect of *Cucumis sativus* n-butanol fraction on body weight

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test.*p<0.05, **p<0.01 vs Diabetic Control.

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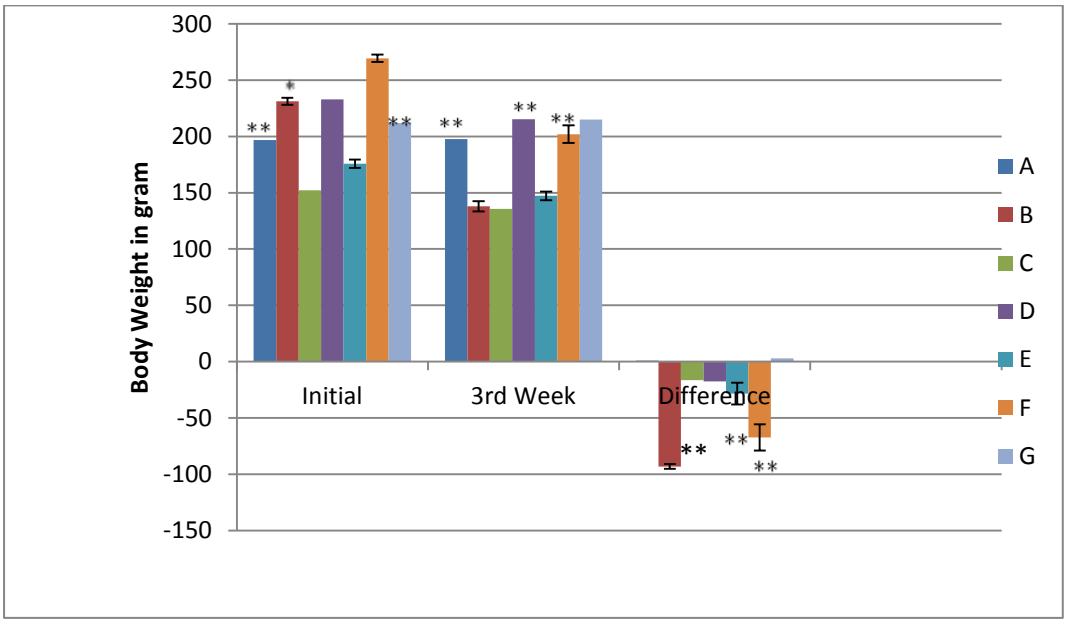

Fig No. 3: Effect of *Cucumis sativus* on body weight

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test.*p<0.05, **p<0.01 vs Diabetic Control.

3.3 Diabetic Neuropathy:

Group	Treatment
A	Normal Control
B	Diabetic Control
C	Diabetic + Gbapentin(100 mg/kg)
D	Diabetic + N-butanol fraction of *Cucumis sativus*(10 mg/kg)
E	Diabetic + N-butanol fraction of *Cucumis sativus*(25 mg/kg)
F	Diabetic + N-butanol fraction of *Cucumis sativus*(50 mg/kg)
G	Non-Diabetic + N-butanol fraction of *Cucumis sativus*(25 mg/kg)

Table No.8: Experimental Design for Neuropathy

3.4. Thermal hyperalgesia

3.4.1. Tail Flick Test

Group	Tail withdrawal latency (sec)
A	2±0.316**
B	12.2±1.068**
C	4.6±0.678**
D	6.6±0.400**
E	6.8±0.374**
F	6.6±0.400**
G	2.6±0.678**

Table No. 9: Effect of *Cucumis sativus* n-butanol fraction on Tail Flick Test:

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Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test.**p<0.01 vs Diabetic Control

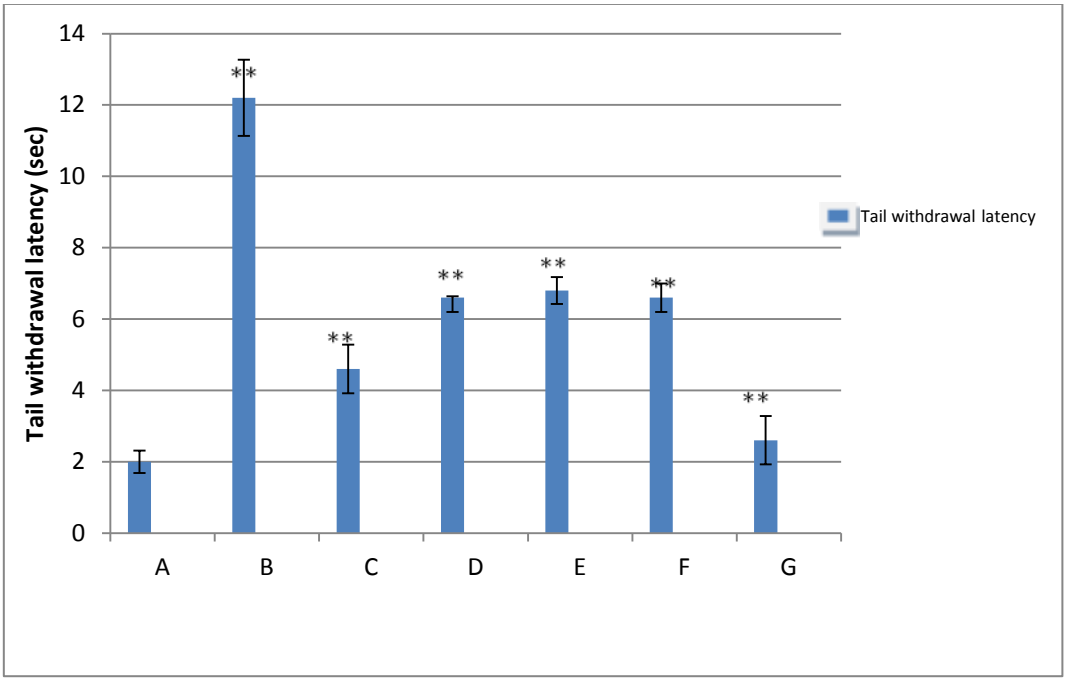

Fig No 4: Effect of *Cucumis sativus* on Tail Flick

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test. **p<0.01 vs Diabetic Control**.**

3.5. Hot Plate Test

Group	Paw withdrawal latency (sec)
A	7.2±1.068
B	14.4±1.030
C	8.6±0.678**
D	9.2±2.0.583**
E	13.2±0.800
F	9.6±0.678**
G	6.2±1.356**

Table No. 10 : Effect of *Cucumis sativus* n-butanol fraction on paw withdrawal latency:

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test. **p<0.01 vs Diabetic Control.

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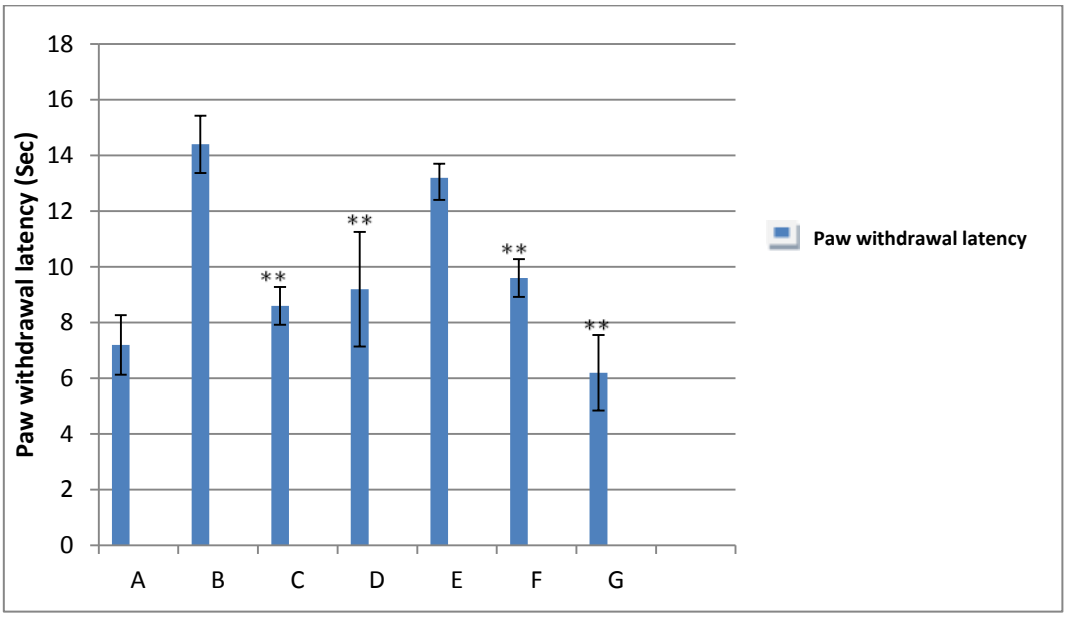

Fig No 5 : Effect of *Cucumis sativus* on paw withdrawal latency

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test. **p<0.01 vs Diabetic Control

3.5. Rota rod

Group	Paw withdrawal latency (sec)
A	193±14.883
B	25.4±3.265
C	125.2±22.32**
D	54.4±15.608**
E	90±20.28
F	117.2±18.24**
G	130.8±21.85**

Table No.11: Effect of *Cucumis sativus* n-butanol fraction on fall of time in rota rod test.

Data is presented as Mean ± SEM (n=5) One way analysis of varience (ANOVA) followed by Dunnet's test. **p<0.01 vs Diabetic Control.

4. CONCLUSION

The effects of Cucumis sativus n-butanolic fraction of methanolic extract on STZ-induced hyperglycemia and diabetic neuropathy in rats are examined in the current study. The study's findings demonstrate that BFCS improves body weight in a time- and dose-dependent manner while dramatically lowering blood glucose levels. Thermal hyperalgesia (Hot plate, Tail flick), as well as Motor Incoordination (Rota rod test), are models of diabetic peripheral neuropathy that were researched. The heat and mechanical hyperalgesia were dramatically reduced by the BFCS. However, the time on the rotarod test has fallen significantly, showing a significant increase. As a result of improvements in myelination and the restoration of neuronal integrity, the saponin from Cucumis sativus showed considerable therapeutic and preventive effects on diabetic neuropathy, consequently slowing the disease's course.

The BFCS has antidiabetic effect in STZ-induced diabetes and improves diabetic neuropathy in rats, in conclusion.

5. FUTURE PROSPECTIVE

The n-butanolic fraction of the methanolic extract of Cucumis sativus shown anti-diabetic activity in the current study's STZ-induced diabetes. So it's crucial to continue fractionating, isolating, and identifying active ingredients. Various animal models in various diabetic conditions will be used to examine the active principle

for its antidiabetic and neuroprotective impact activity. Finding the neuroprotective effects' mechanism of action is equally crucial. Finding the drug's effects in other neuropathic disorders is crucial because the current trial demonstrated its effectiveness in diabetic neuropathy.

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