"Neuroprotective and Antidiabetic Effects of a Novel Polyherbal Extract in High-Fat Diet/STZ-Induced Diabetic Neuropathy in Rats"

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Abstract

Diabetic neuropathy (DN) is a progressive nerve disorder caused by diabetes, characterized by chronic high blood sugar that leads to nerve inflammation and damage, resulting in pain, numbness, and loss of sensation. Current synthetic therapies often produce adverse effects such as hypoglycaemia, weight fluctuations, and organ toxicity, which hinder patient compliance and increase interest in herbal alternatives. This study evaluated a novel polyherbal extract (PHE) against diabetic neuropathy induced by a high-fat diet and streptozotocin (HFD-STZ) in rats. The PHE was prepared in a 2:2:1 composition ratio by decoction method. In the rat model, subjects received different doses of PHE (100, 200, and 400 mg/kg p.o) or gabapentin (300

mg/kg p.o) for 45 days. At the highest dose of 400 mg/kg, PHE significantly alleviated neuropathic symptoms, as shown by reduced mechanical allodynia and thermal hyperalgesia. It also improved glycemic control, normalized lipid profiles, and decreased oxidative stress markers by lowering lipid peroxidation while increasing levels of glutathione, superoxide dismutase, and catalase. Additionally, PHE enhanced gastric emptying time and exhibited neuroprotective effects by preserving the architecture of the sciatic nerve. In MIN6 β-cells, PHE maintained cell viability and stimulated glucose-dependent insulin secretion, highlighting its therapeutic potential for managing diabetic neuropathy.

Keywords: Diabetic neuropathy, polyherbal formulation, antioxidant, anti-inflammatory, neuroprotection.

Introduction

Diabetic neuropathy (DN) is a serious scenario linked to diabetes, primarily caused by chronic hyperglycaemia [1]. Current estimates suggest that by 2050, around one-third of the global population, projected to be 9.7 billion, may have diabetes, with approximately 50 % of these affected likely to experience diabetic neuropathy [2]. The etiology of DN is due to complex interactions between metabolic, vascular, and neural factors, primarily triggered by chronic hyperglycaemia. This leads to insulin resistance and dyslipidaemia, causing peripheral nerve damage and microvascular dysfunction, which impairs nerve signalling and worsens neural ischemia [3].

Current diabetic neuropathy management focuses on glycaemic control and targeted therapies, including ROS inhibitors, aldose reductase inhibitors, and PKC inhibitors for the underlying mechanism in DN [4], along with SNRIS, anticonvulsants, and NMDAR antagonists for symptom relief [5]. However, these drugs often cause adverse effects like hypoglycaemia, weight changes, and organ toxicity, which have led to a decline in patient trust. Because of this, more people around the world are turning to herbal remedies instead of synthetic drugs [6].

Herbal formulations are often preferred because they generally have a better safety profile compared to traditional oral hypoglycaemic agents [7]. Various earlier studies have shown that using a single herb may not be enough to achieve the desired medicinal effect [8], however, combining multiple herbs, known as polyherbalism, can enhance their medicinal properties and reduce toxicity [9]. This approach capitalizes on the complementary pharmacological actions of

different plant compounds, allowing for more comprehensive therapeutic effects with minimized adverse reactions [10]. Several evidence-based herbal formulations, such as Hyponidd, Trasina, Punchparna tincture, Diasulin, and Diamed, have demonstrated effectiveness in managing diabetes, hyperlipidemia, and oxidative stress through their multi-targeted pharmacological actions [11].

Withania somnifera, Gymnema sylvestre, Syzygium cumini, Tinospora cordifolia, Emblica officinalis, Pterocarpous marsupium, Azadirachta indica, and Momordica charantia have all individually demonstrated antidiabetic, antihyperlipidemic, and antioxidant activities. However, there is no scientific data have been reported on their synergistic effects in DN, hence current investigation assesses the effects of polyherbal extract (PHE) all the above herbs together on a high-fat diet (HFD) and streptozotocin (STZ) induced diabetic neuropathy in experimental animals.

Materials and Methods

Material

Collection and authentication of plants material

Based on literature, plants which have been reported to possess antidiabetic, antihyperlipidemic, anti- inflammatory and antioxidant activities these plants are selected. The plant sample were collected fresh, while the other herbs were procured from an ayurvedic shop in Malegaon. All gathered plant samples were authenticated by the Department of Botany and the Research Centre, M.S.G. Arts, Science, and Commerce College to ensure their botanical authenticity (MSG/PG/BOT-105 04/12/2024). STZ was obtained from Otto Chemie Laboratory, Gabapentin was obtained as gift sample from SYMED LAB limited, Hyderabad.

Methods

Preparation of polyherbal extract

The plant parts were air-dried and pulverized using a mechanical grinder. For the preparation of extracts, decoction techniques were employed~~. The,~~ powdered herbs were mixed in a specific ratio of 2:2:1, comprising two parts from five herbs, two parts from two herbs, and one part from the remaining herb (w/w) to achieve a homogeneous blend as detailed in Table 2 [11]. The extraction process involved mixing the dry powder with 100 ml of distilled water, heating the mixture to a boil, then reducing the heat to allow the volume to concentrate to half (50 mL). The concentrated mixture was filtered using whatman paper. The resulting filtrate was boiled again to produce a more concentrated extract, which was subsequently dried. The dried extracts were preserved in an airtight container and kept in the refrigerator, and used for pharmacological experiments [12].

Table 1: The polyherbal extract contains bioactive phytochemicals with diverse pharmacological properties.

Plant	Phytochemicals	Pharmacological properties	Reference
Withania somnifera	Isopellertierine, anferine, withanolides, withaferins.	Antihyperglycemic, Anti-inflammatory, Antioxidant	[13] [14]
Gymnema sylvestre	Hentriacontane, pentatriacontane, flavones, gymnemasaponins, and gymnemic acids.	Antidiabetic Anti-inflammatory	[15] [16]
Azadirachta indica	Azadirachtin, nimbin, nimbidin, gedunin, salannin, quercetin, beta-sitosterol, limonoids, flavonoids, triterpenoids, nimbolide, margolone, cyclic peptides	Anti-inflammatory, Antidiabetic, Antioxidant,	[17] [18]
Tinospora cordifolia	Aporphine alkaloids, tinosporides, berberine, palmatine, magnoflorine, tinosporine, tetrahydropalmatine, isocolumbine,and choline	Antidiabetic, Anti-inflammatory, Antioxidant	[19] [20] [21]
Syzygium cumini	Jambosine, anthocyanins, gallic acid, ellagic acid, corilagin, quercetin, kaempferol, myricetin, oleanolic acid,	Antidiabetic, Antioxidant, Anti-inflammatory,	[22]

	betulinic acid, friedelin, β-sitosterol, triterpenoids, tannins, flavonoids.		
Emblica officinalis	Phyllaemblic acid, quercetin, kaempferol, luteolin, apigenin, tannins, gallic acid, ellagic acid, geraniin, and vitamic C	Antioxidant, Antidiabetic, Anti-inflammatory.	[23] [24]
Pterocorous marsupium	Marsupsin, pterostilbene, liquirtigenin, hydroxyflavanone, P-hydroxybenzaldehyde	Antioxidant, Antidiabetic, Anti-inflammatory.	[25] [26]

Table 2: Polyherbal extract composition

Name of plant	**Family**	**Part used**	**Weight (g)**
Withania somnifera	*Solanaceae*	Root	15
Gymnema sylvestre	*Asclepiadaceae*	Fruit	15
Azadirachta indica	*Meliaceae*	Leaves	15
Tinospora cordifolia	*Menispermaceae*	Stem	15
Momardica charanita	*Cucurbitaceae*	Fruit	15
2 parts of the above herbs			
Syzygium cumini	*Myrtaceae*	Seeds	10
Emblica officinalis	*Phyllanthaceae*	Fruit	10
2 parts of the above herbs			
Pterocorous marsupium	*Fabaceae*	Stem	5
1 part of the above herb			

In *vivo* studies

Experimental animals and study design

Adult male wistar rats (180-200 g) were obtained from Lacsmi Biofarm Pvt. Ltd. in Pune, India and the study protocol was approved (KBH/IAEC/2024/12-04) by the Institutional Animal Ethics Committee of K.B.H.S.S. Trust's Institute of Pharmacy, Malegaon. Diabetes was induced in rats by HFD and low dose of STZ (35mg/kg, i.p.), then, after 4 weeks the rats with glucose level above 300 mg/dl were randomly divided into six group (n=6).

In which the first group comprised of non-diabetic rats whereas the rest of the groups include diabetic rats. The normal control group (G1NC) and diabetic control group (G2DC) did not receive any treatment but were allowed free access to distilled water. The third group (G3S) diabetic rats received standard drug Gabapentin orally at the dose 300 mg/kg in 1% normal saline solution. The groups four, fifth and sixth diabetic rats were treated with polyherbal extract (p.o.) at doses: PHE-I (100 mg/kg), PHE-II (200 mg/kg), and PHE-III (400 mg/kg) respectively. During the study period of 45 days non-diabetic rats received standard chow diet, while diabetic rats were fed a HFD with ad libitum water.

Behavioral estimations

In diabetic neuropathy, various behavioral parameters like mechano-tactile allodynia (using the Von Frey hair test, Aesthesio, DanMic Global LLC, USA) [27], and thermal hyperalgesia (using tail immersion and hot plate tests, Eddy hot plate, Omega India) [28,29] were assessed on the 0^{th}, 22^{nd}, and 45^{th} day of the treatment schedule.

Biochemical parameters in blood and tissue homogenate

Blood was collected and serum was separated for various biochemical markers, including glucose, triglyceride, total cholesterol, HDL-C, and LDL-C, using Merilizer Auto Quant 100 Amara, commercial diagnostic kits (Meril Diagnostics Pvt. Ltd, India). Rats were sacrificed, and the sciatic nerves were rapidly excised. Sciatic nerve tissue was homogenized in 0.1 M Tris-HCL buffer (pH 7.4). The resulting supernatant was analyzed for lipid peroxidation (LPO) [30], glutathione (GSH) [31], superoxide dismutase (SOD) [32], catalase (CAT) [33], and TNF-α levels using ELISA (SciTesla, Mumbai).

Gastric emptying time

Gastric emptying was assessed using a phenol red method. Animals were administered 0.3 ml of phenol red test meal by oral gavage and euthanized 20 minutes later. The stomach was then isolated and homogenized with its contents in 25 ml of 0.1 N NaOH. After settling for 1 hour at room temperature, 8 ml of the supernatant was combined with 1 ml of 33% trichloroacetic acid to precipitate proteins. The mixture was centrifuged at 1600g for 30 minutes, and 2 ml of 2N NaOH was added to the resulting supernatant. The final homogenate was measured for absorbance at 560 nm [34].

Histopathological assessment of the sciatic nerve.

The sciatic nerve was randomly isolated, preserved in 10% formalin, and sent to the SciTesla laboratory, Mumbai, for histopathological examination.

***In vitro* studies**

MIN6 Cell culture

Dulbecco's Modified Eagle Medium (DMEM) with 25 mmol/L glucose was used to grown MIN6 cells. The conditions were kept at 37 ^{0}C and 5 % CO_2 in 95% air. 15% fetal calf serum, 50 mg/L penicillin sulfate were added to the medium. The MIN6 cells used in this study were collected between passages 16 and 23.

Cell viability assay

Cell viability was assessed using the 3-(4,5-Dimethylthiazol-2yl)-2,5-Diphenyltetrazolium Bromide (MTT) test. Thirty thousand MIN6 cells were initially incubated into 96- well plates and allowed to adhere overnight. The cells were then treated with PHE at concentration of 10, 40, and 100 µg/ml and incubated for 72 hours. Next, a 20-microliter solution of MTT at a concentration of 5 mg/ml was added to each well and incubated to each well and incubated for 4 hours. Subsequently, 100 microliters of dimethyl sulfoxide (DMSO) were employed to solubilise the formazan crystals produced during MTT reduction. Plates were gently agitated for 10 seconds to achieve complete dissolution, and absorbance was measured at 450 nm using an ELISA microplate reader (Benesphere 21) [35].

Insulin Secretion assay

The experiment on β- cell insulin secretion included placing roughly 3×10^4 MIN6 cells per well in 6-well plates.

During the study, the cells were incubated for 60 minutes under with only Krebs-Ringer bicarbonate buffer (KRB) (135 mmol/1 Nacl, 5 mmol/1 KCL, 1 mmol/1 $MgSO_4$, 0.4 mmol/1 K_2HPO_4, 11 mmol/1 Glucose, 20 mmol/1 HEPES, pH 7.4), KRB containing glucose at 11 mM glucose (hyperglycaemic conditions). PHE was administered at a concentration of 1000 µg/mL to assess its effect on insulin secretion, while Glibenclamide was used at a concentration of 10 µM. Following the 60-minute incubation period, aliquots from each well were collected into Eppendorf tubes and centrifuged at 4000 g for 5 minutes at 4˚C. The insulin levels were then analysed using C-peptide kits [36].

Statistical analysis

Data were expressed as the mean with a standard deviation (SD). The analysis was conducted

using GraphPad Prism version 8.4.2 software. Behavioural test results were analysed using two-way analysis of variance (ANOVA), while one-way ANOVA was utilised to evaluate data on blood and tissue indicators. Bonferroni's multiple range test was employed for analysis.

Results

Effect of aqueous polyherbal extract on body weight

The rats administered with the aqueous polyherbal extract (PHE) at varying doses (100,200, and 400 mg/kg) exhibited a dose-dependent increase in body weight compared to DC (Figure 1).

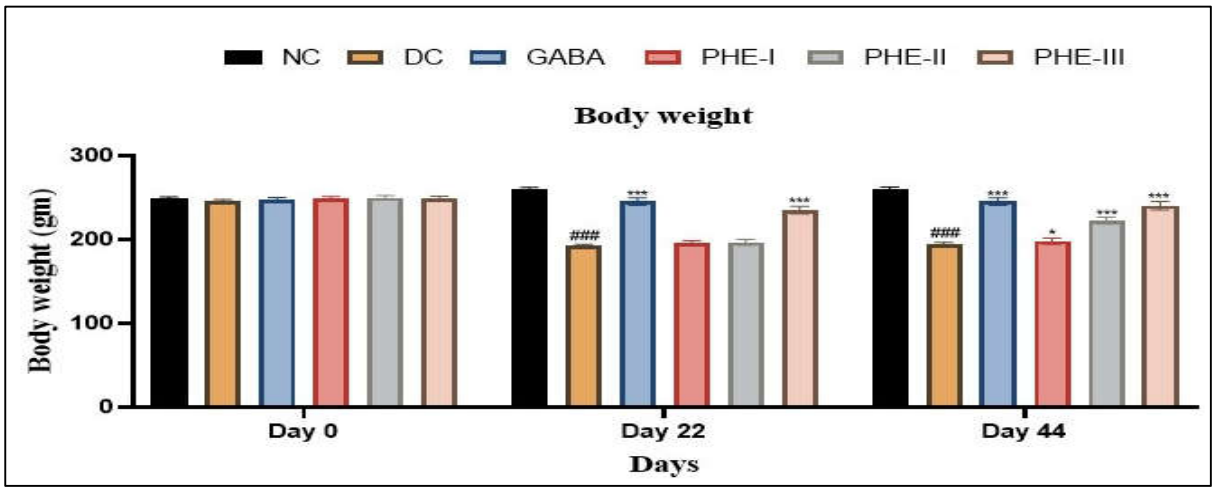

Figure 1: Effect of aqueous PHE on body weight in diabetic rats.

Data are represented as means ± SD (n=6/group). Two-way ANOVA followed by the Bonferroni test for multiple comparisons. ###P< 0.001 when compared to normal control (NC) *p<0.05, ***p < 0.001 when compared to diabetic control (DC).

Effect of aqueous polyherbal extract on mechano-tactile allodynia (Von Frey hair test) in diabetic rats.

The paw withdrawal threshold (PWT) ~~indicates no significant variance between DC rats and NC rats (P>0.05) one day before the diabetes induction. However,~~ from days 22 to 44, ~~the PWT~~ markedly diminished in the diabetic rats (###P < 0.05~~).~~) as compared to NC. Additionally, PHE administration resulted in dose-dependent increases in PWT at doses of 100, 200 and 400 mg/kg when compared to the ~~untreated~~ DC rats (*p < 0.05, *** p < 0.001) (~~see~~Figure 2A).

Effect of aqueous polyherbal extract on thermal hyperalgesia (Hot plate test and Tail immersion test) in diabetic rats.

The significant reduction (### P<0.05) in both PWL and TWL was observed in DC rats from day 22 to day 44. Administration of PHE at doses of 100, 200, and 400 mg/kg progressively enhanced both PWL and TWL compared to the DC, demonstrating a marked improvement in thermal hyperalgesia (*p< 0.05, **p< 0.01, ***p<0.001) (Figures 2B and 2C).

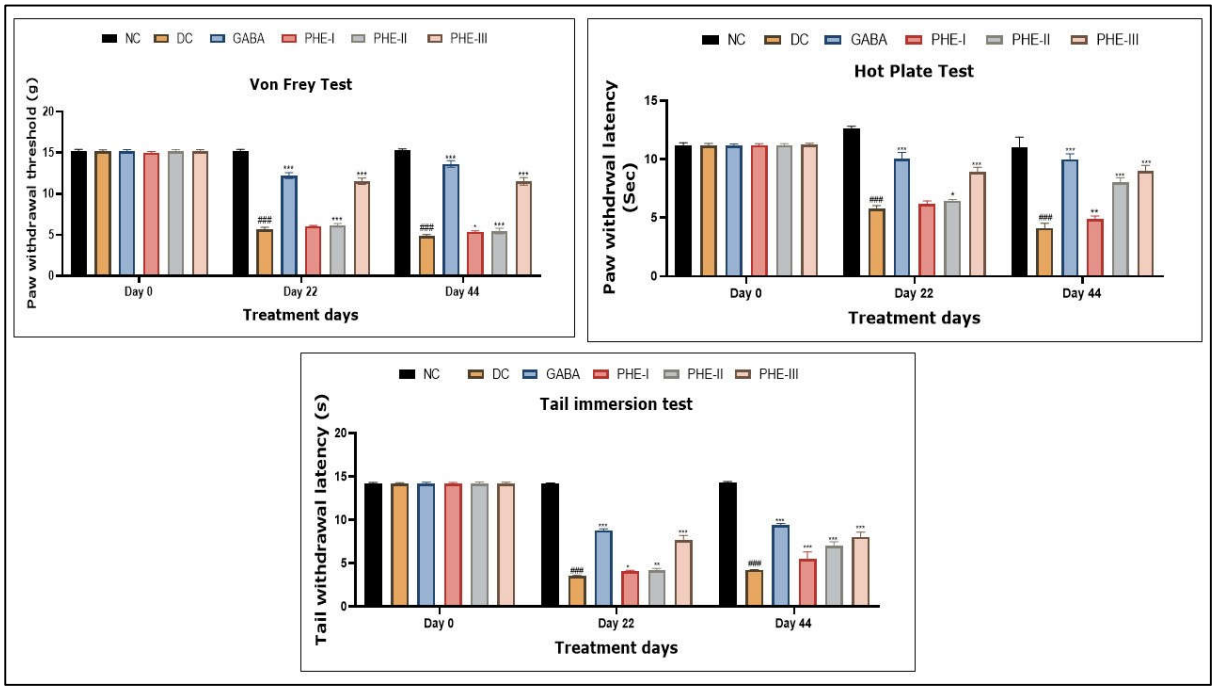

Figure. 2: Effect of aqueous polyherbal extract on mechano-tactile allodynia (Von Frey hair test) (A) and Thermal hyperalgesia (Hot plate and Tail immersion test) (B and C) in diabetic rats.

Data are presented as means ± SD (n=6/group). Two-way ANOVA followed by the Bonferroni test for multiple comparisons. ### P<0.001 when compared to NC, *p< 0.05, **p< 0.01, ***P<0.001 when compared to DC.

Effect of aqueous polyherbal extract on serum biochemical parameters in diabetic rats.

The diabetic group exhibited significantly lower levels of HDL cholesterol and higher levels of glucose, LDL, TC, and TG compared to normal controls (### P<0.001). PHE at doses of 100, 200, and 400 mg/kg significantly improved hyperglycaemia and lipid profile abnormalities compared to the DC group (*p< 0.05, **p< 0.01, *** P<0.001) (Table 3).

Table 3: Effect of an aqueous polyherbal extract on the biochemical estimation in diabetic rats.

Parameters	NC	DC	GABA	PHE-I	PHE-II	PHE-III
Glucose (mg/dL)	92.67±1.36	257.5± 4.63###	212.0± 2.44***	249.7± 1.36*	238.0± 1.41***	188.5± 8.57***
TC (mg/dL)	110.2 ± 5.94	197.6 ± 3.31###	115.4 ± 6.84***	190.8 ± 1.47	182.3 ± 2.73***	143.5 ± 3.61***
TG (mg/dL)	107.5 ± 2.15	186.5±3.27###	98.3 ± 6.11***	178.5 ± 1.87**	168.2 ± 4.46***	110.5 ± 2.25***

LDL-C (mg/dL)	29.85 ± 2.60	65.34 ± 2.06$^{###}$	36.41 ± 3.74***	61.84 ± 1.72	58.68 ± 1.17**	35.56 ± 3.94***
HDL-C (mg/dL)	55.6 ± 3.4	27.40 ± 1.53$^{###}$	52.8 ± 3.2***	31.10 ± 0.88*	34.18 ± 1.71***	47.31 ± 1.54***

NC– Normal control, DC– Diabetes control, GABA– Standard (Gabapentin), PHE- Polyherbal extract -I, II, III. Data are presented as means ± SD (n=6/group)—One-way ANOVA followed by the Bonferroni test for multiple comparisons. ###p< 0.001when compared to normal control (NC); *p< 0.05, **p< 0.01, ***p< 0.001 when compared to diabetic control (DC).

Effect of aqueous polyherbal extract on oxidative stress and inflammatory marker in diabetic rats.

Diabetic rats showed markedly increased oxidative stress markers, including elevated LPO and inflammatory marker, including TNF- α and significantly decreased levels of GSH, SOD, and CAT, in comparison to normal controls ($^{###}P < 0.001$). PHE at 100, 200 and 400 mg/kg produced dose-dependent, significantly reduced LPO and increased GSH, SOD, and CAT levels. Additionally, inflammatory markers, specifically TNF-α, were reduced compared to DC (*p< 0.05, **p< 0.01, ***P< 0.001) (Table 4).

Table 4: Effect of aqueous polyherbal extract on oxidative stress markers and TNF-α levels in diabetic rats.

Parameters	NC	DC	GABA	PHE-I	PHE-II	PHE-III
LPO (nM/mg protein)	3.30 ± 0.88	10.29 ± 0.82$^{###}$	4.85 ± 1.04***	8.45 ± 0.92*	7.77 ± 1.34***	4.93 ± 1.04***
GSH (µg/mg protein)	2.20 ± 0.50	0.64 ± 0.06$^{###}$	2.07 ± 0.56***	0.83 ± 0.05	1.32 ± 0.07**	1.82 ± 0.25***
SOD (U/mg protein)	22.83 ± 1.49	8.35 ± 1.07 $^{###}$	19.53 ± 1.08***	8.35 ± 0.68	10.67 ± 1.18**	16.63 ± 1.03***
CAT (U/mg protein)	51.30 ± 3.23	19.55 ± 1.37$^{###}$	45.63 ± 3.67***	23.23 ± 0.57*	24.38 ± 1.37**	42.15 ± 1.39***

TNF-α (Pg/ml)	56.28 ± 2.29	184.3 ± 4.09$^{###}$	105.2 ± 3.77***	178.4 ± 1.37**	116.2 ± 3.11***	84.88 ± 2.00***

NC– Normal control, DC– Diabetes control, GABA– Standard (Gabapentin), PHE- Polyherbal extract -I, II, III. Data are presented as means ± SD (n=6/group). One-way ANOVA followed by the Bonferroni test for multiple comparisons. $^{###}$ P<0.001 when compared to NC, *p< 0.05, **p< 0.01, ***P<0.001 when compared to DC.

Effect of aqueous polyherbal extract on gastric emptying time in diabetic rats.

Diabetic animals showed significantly delayed gastric emptying times compared to healthy controls ($^{###}$P< 0.001). PHE at doses (100, 200 and 400 mg/kg) resulted in progressively enhanced gastric emptying time compared to DC (*p< 0.05, **p< 0.01, ***P< 0.001) (Figure 3).

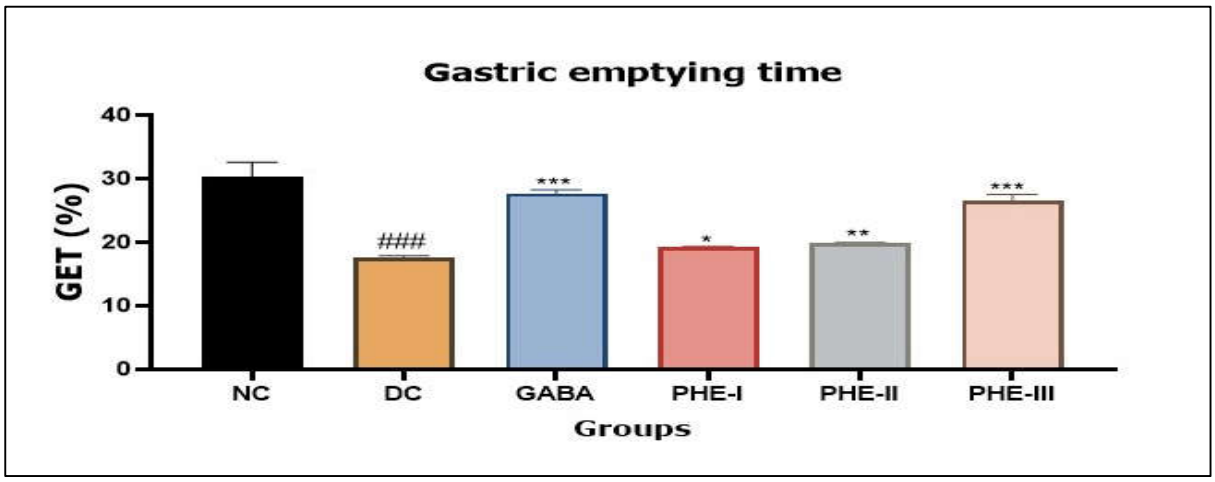

Figure 3: Effect of aqueous polyherbal extract on gastric emptying time in diabetic rats. Data are presented as means ± SD (n=6/group). One-way ANOVA followed by the Bonferroni test for multiple comparisons. ### P<0.001 when compared to NC, *p< 0.05, **p< 0.01, ***P< 0.001 when compared to DC.

Effects of aqueous polyherbal extract on cell viability assays in MIN6 cell line

We examined the effect of a polyherbal extract on cell viability using the MTT assay. The normal control group maintained optimal cell viability, but H_2O_2 treatment significantly reduced it. The PHE at 10, 40, and 100 µL showing dose-dependent enhanced cell viability compared to the H_2O_2 group (See Table 5).

Table 5: Effect of aqueous polyherbal extract on cell viability against the MIN6 cell line.

Sr. No	**Concentration (µg/ml)**	**Absorbance**				**Cell viability**
		1	**2**	**3**	**Average**	
1.	**Control**	1.596	1.598	1.599	1.597	85.09

2.	**H_2O_2 induced (0.4 mM)**	0.426	0.441	0.435	0.434	27.17
3.	**PHF-I (10 µg/ml)**	0.633	0.639	0.637	0.636	39.82
	PHF-II (40 µg/ml)	0.955	0.953	0.951	0.953	59.64
	PHF-III (100µg/ml)	1.263	1.261	1.262	1.262	78.99

Effects of aqueous polyherbal extract on insulin secretion assays (MIN6 cell line)

The polyherbal extract demonstrated glucose-responsive insulinotropic effects in MIN6 β-cells cultured under hyperglycaemic conditions (11 mM glucose). At a dosage of 1000 µg/mL, the treatment resulted in a notable insulin release of 2.12 µU/mL and a corresponding C-peptide secretion of 6.47 pmol/mL, compared to control levels of 1.46 pmol/mL C-peptide. While its secretory potency was lower than that of the standard drug glibenclamide (10 µM; 3.32 µU/mL insulin, 9.97 pmol/mL C-peptide), the extract displayed relevant insulinotropic activity.

Table. 6: Effect of sample-PHE in insulin secretion in MIN6 cell line

Sr no.	**Compounds**	**Concentration**	**C Peptide secretion (pmol/ml)**	**Insulin secretion (µU/ml)**
1	Control	10 µM	01.46	
2	Standard (Glibenclamide)	10 µM	9.97	3.32 µU/ml
3	Polyherbal extract	1000 µg/mL	6.47	2.12µU/ml

Calculation- 1 pmol /ml C peptide ~ 0.333 µU/ml Insulin

So, c peptide level- 6.47 pmol/ml Insulin level ~ 6.47 pmol/ml *0.333 = 2.12µU/ml

Effect of aqueous polyherbal extract on sciatic nerve histology in diabetic rats

Figure 4 shows intact sciatic nerve morphology in normal controls (NC), while diabetic controls (DC) displayed severe damage, including neuronal degeneration, inflammation, and edema. Treatment with polyherbal extract (100, 200, and 400 mg/kg) significantly reduced these abnormalities compared to DC. These results underscore the enhanced efficacy of the PHE in managing diabetic neuropathy, likely attributed to its improved bioavailability and combined antioxidant and anti-inflammatory properties.

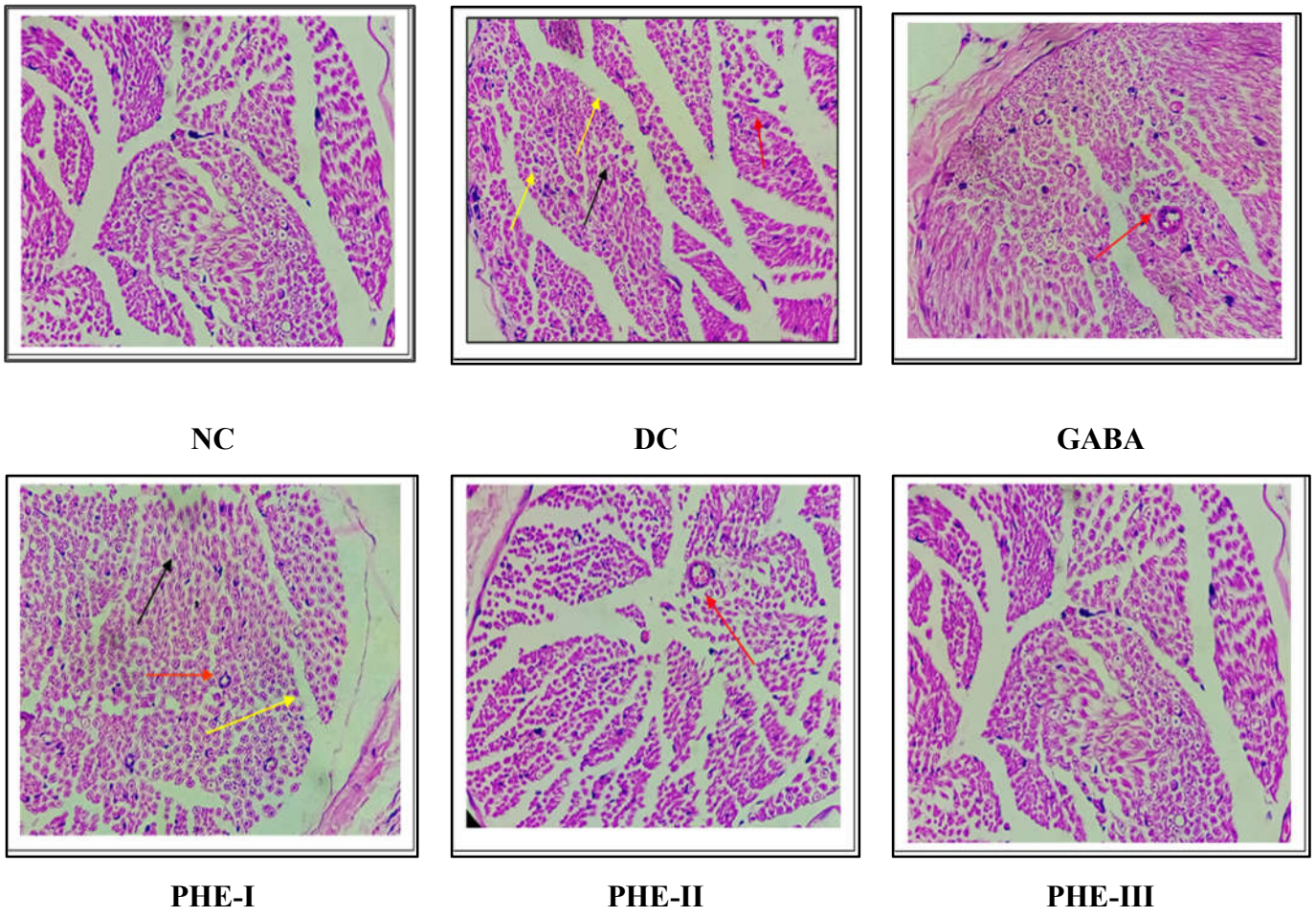

Figure 4. Effect of aqueous polyherbal extract on histopathological changes of sciatic nerve in rats. Histopathological image of sciatic nerve sections from rats stained with H&E (100×). Degeneration (black arrow), **Discussion**

The HFD-STZ model is a validated and widely utilised method for inducing diabetes, and it has proven to be highly effective in inducing DN [37].

The rodent model of diabetic neuropathy used is the HFD-STZ model, which uses a HFD to cause insulin resistance coupled with the destruction of beta cells by STZ, leading to extreme hyperglycaemia [38]. A polyherbal extract reduces blood glucose may be due to inhibiting α-amylase/α-glucosidase [39,40] and activating GLUT4 translocation [41] and AMPK signaling, thereby enhancing peripheral insulin sensitivity and restoring metabolic balance [42].

Hyperglycaemia affects the use of glucose in the body and, such as, results in the catabolism of fats and structural proteins, especially muscle, to provide energy requirements [43]. This is the breakdown of protein that leads to progressive weight loss and is one of the indicators of uncontrolled diabetes, where the catabolism of protein is enhanced, and nitrogen is lost [44]. Polyherbal extract that effectively address glucose metabolism problem may be due to inhibition of α-glucosidase and α-amylase, and protection of proteins as well as increasing lipid production

via synergistic phytochemicals [45]. It is a multi-faceted treatment mode that strives to provide metabolic balance and provoke weight regain in diabetes-related weight loss [46].

DN is linked to a reduced pain threshold, which has been demonstrated through behavioral nociceptive assessments. Mechanical allodynia was assessed in this study by Von Frey hair test [47], thermal hyperalgesia by Eddy hot plate, and the tail immersion test [48]. The polyherbal extract raising the pain threshold, may be due to increasing insulin sensitivity and maintaining the functioning of the pancreatic β- cells. This will help to deal with the underlying metabolic disturbances which play a part in neuropathy development [49].

Dyslipidaemia is a common issue in those with type 2 diabetes, characterized by elevated levels of TC, TG and LDl-C, along with reduced levels of HDL-C. This condition poses a great risk to cardiovascular diseases [50]. A polyherbal extract is proven to be significantly effective in reducing the levels of TC, LDL-C and TG and raising the levels of HDL-C as compared to DC. This beneficial action may be due to inhibition of hepatic HMG-CoA reductase that lessens cholesterol production [51], and stimulation of the PPAR-gamma pathway, which augments lipid metabolism and ameliorates cardiovascular risk factors [52].

Oxidative stress occurs when excess reactive oxygen species (ROS) exceed the body's antioxidant defenses, facilitating to diabetic neuropathy through a process called lipid peroxidation, as evidenced by elevated levels of malondialdehyde (MDA) [53]. Additionally, ROS suppress the activity of SOD and decrease levels of GSH and CAT [54,55,56]. The polyherbal extract was observed to have an anti-oxidative effect, which may be due to the activation of the Nrf2/HO-1 pathway [57], suppressed NF-kB, ROS scavenging capacity, metabolic chelation, and maintenance of mitochondrial integrity. These activities assist in recuperating the levels of antioxidant enzymes and alleviate LPO [58].

In diabetic neuropathy, hyperglycaemia activates the TLR4/MyD88 signaling pathway, leading to the release of the pro-inflammatory cytokine NF-kB and an increase in TNF-alpha [59]. These activities result in nerve injury. The polyherbal extract has an ameliorating effect on inflammation, likely due to the inhibition of TLR4/MyD88 signaling [60],and the suppressed activity of NF-kB. This mechanism reduces the level of TNF-alpha, provides neuroprotection, and enhances nerve conduction [61].

Diabetic neuropathy HFD-STZ induced gastroparesis is a delay in gastric emptying that occurs in response to sustained hyperglycaemia [62]. The polyherbal extract improves gastric transit, which may be due to restoring the vagal tone, supports interstitial cells and improves the contractility of smooth muscle [63].

This study systematically assessed the therapeutic effect of a polyherbal extract on pancreatic β-cells function in MIN6 cells. When MIN6 β-cells are exposed to H_2O_2, they produce

excessive ROS that exceed their antioxidant defences, leading to oxidative damage and reduced cell viability. However, treatment with a polyherbal extract significantly restored cell survival, likely by activating the Nrf2/HO-1 antioxidant pathway [61], additionally, the administration of the polyherbal extract enhanced glucose stimulated insulin secretion (GSIS) in MIN6 cells, possibly due to its effect on insulin receptor mediated signalling cascades, resulting in PI3K/AKT-mediated enhancement of glucokinase activity and improved glucose phosphorylation efficiency [64].

The anti-diabetic effects of phytoconstituents are mediated via different but interlinked molecular pathways that involve inhibition of key proteins in glucose regulation and control of metabolism [65]. Taken together, this multi-target mechanism highlights the synergistic anti-diabetic effect of polyherbal extract in the management of type 2 diabetes mellitus through concomitant regulation of glucose metabolism, insulin sensitivity, oxidative stress, and inflammation.

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