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Evaluation of the Antidiabetic Activity of Hydroalcoholic Extract of Niruris indica (HENI) and HENI-Loaded Phytosomes in Streptozotocin–Nicotinamide Induced Diabetic Rats

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Abstract:

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Although herbal medicines possess significant antidiabetic potential, their therapeutic efficacy is often limited by poor bioavailability. Phytosome technology has emerged as an effective strategy to enhance the absorption and biological activity of plant-derived compounds. The present study evaluated the antidiabetic activity of the hydroalcoholic extract of Niruris indica (HENI) and HENI-loaded phytosomes in streptozotocin–nicotinamide-induced diabetic Wistar rats. HENI-loaded phytosomes were prepared using the antisolvent precipitation method and evaluated for acute toxicity, blood glucose, body weight, lipid profile, liver function markers, and stability. Both HENI and HENI-loaded phytosomes were found to be safe up to 2000 mg/kg. Treatment significantly ($p < 0.05$) reduced blood glucose levels, improved body weight, normalized lipid profile, and restored liver biochemical parameters compared with diabetic control rats. The phytosomal formulation exhibited greater therapeutic efficacy than the plain extract and remained stable under accelerated and room-temperature storage conditions for three months. These findings suggest that HENI-loaded phytosomes represent a promising herbal nanocarrier system for improving the management of diabetes mellitus.

Keywords: Niruris indica, phytosomes, diabetes mellitus, streptozotocin, hydroalcoholic extract, nanotechnology.

Introduction:

Diabetes mellitus is a major metabolic disorder characterized by chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or both. The disease is associated with abnormalities in carbohydrate, lipid, and protein metabolism and can lead to serious complications affecting the liver, kidneys, cardiovascular system, and nervous system (American Diabetes Association, 2024). Despite the availability of several antidiabetic drugs, their long-term use may be associated with adverse effects, encouraging the search for

safer and more effective alternatives (Davies et al., 2022).

Medicinal plants are rich sources of bioactive compounds such as flavonoids, phenolics, tannins, and alkaloids that exhibit antihyperglycemic, antioxidant, and hypolipidemic activities (Ekor, 2014). However, many phytoconstituents show poor oral bioavailability because of limited solubility and absorption. Phytosome technology enhances the bioavailability of herbal constituents by forming phospholipid complexes, thereby improving their therapeutic efficacy (Semalty et al., 2009).

Niruris indica is traditionally used for the treatment of various disorders and contains several phytochemicals with reported antioxidant and antidiabetic properties. However, limited information is available regarding the antidiabetic efficacy of its phytosomal formulation. Therefore, the present study was undertaken to compare the antidiabetic activity of the hydroalcoholic extract of Niruris indica (HENI) and HENI-loaded phytosomes in streptozotocin–nicotinamide-induced diabetic rats by evaluating blood glucose, body weight, lipid profile, liver function markers, and formulation stability.

Materials and Methods

Collection and Authentication of Plant Material

Fresh aerial parts of Niruris indica were selected for the present investigation based on its reported traditional use in the management of diabetes mellitus and associated metabolic disorders. The plant material was procured from Vindhya Herbals (MFP-PARC), Bhopal, Madhya Pradesh, India, during February 2019. The collected material was thoroughly cleaned to remove foreign matter and subsequently shade-dried under ambient laboratory conditions until a constant weight was achieved. The dried material was coarsely powdered using a mechanical grinder and stored in airtight containers until further use. Proper handling and storage conditions were maintained throughout the study to prevent moisture absorption and degradation of phytoconstituents (Harborne, 1998).

Preparation of Hydroalcoholic Extract of Niruris indica (HENI)

The powdered aerial parts of Niruris indica were initially defatted by maceration with petroleum ether to eliminate fatty substances, chlorophyll, waxes, and other non-polar impurities that could interfere with subsequent extraction. The defatted marc was dried at room temperature and subjected to exhaustive maceration using hydroalcoholic solvent (ethanol:water, 70:30 v/v). Approximately 39 g of powdered plant material was extracted for 72 hours with intermittent shaking to facilitate efficient extraction of phytoconstituents.

The resulting extract was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure at temperatures below the boiling point of the solvent to prevent thermal degradation of bioactive compounds. The concentrated extract was further dried to obtain a semisolid mass and stored in sterile amber-colored airtight containers at 4°C until further use. The percentage yield of the hydroalcoholic extract (HENI) was calculated using the following equation (Bajpai et al., 2012):

Percentage Yield (%) = (Weight of Dried Extract / Weight of Dried Plant Material) × 100

Preparation of HENI-Loaded Phytosomes

HENI-loaded phytosomes were prepared using the antisolvent precipitation method described by Touitou and co-workers with slight modifications (Touitou et al., 2000). Briefly, hydroalcoholic extract,

phospholipid, and cholesterol were mixed in different ratios (1:1, 1:2 and 1:3) to optimize the phytosomal formulation.

The extract-phospholipid mixture was dissolved in 25 mL of dichloromethane and refluxed at 50°C for 3 hours to facilitate complex formation between phospholipids and phytoconstituents. Following solvent evaporation, 20 mL of n-hexane was slowly added under continuous magnetic stirring as an antisolvent, resulting in precipitation of phytosomal complexes.

The precipitated phytosomes were collected by filtration and vacuum dried to eliminate residual organic solvents. The dried phytosomal powder was transferred into amber-colored glass bottles, stored in a desiccator overnight, and preserved at room temperature until further characterization.

Acute Oral Toxicity Study

The acute oral toxicity study was carried out according to the Organisation for Economic Co-operation and Development (OECD) Guideline 423 (OECD, 2002). Healthy Wistar albino rats were fasted overnight before administration of the test formulations.

Animals received different oral doses of HENI and optimized HENI-loaded phytosomes up to a maximum dose of 2000 mg/kg body weight. Following administration, animals were continuously observed during the first four hours for behavioral alterations including tremors, convulsions, salivation, lacrimation, lethargy, grooming behavior, locomotor activity, respiration, and mortality. Daily observations continued for 14 consecutive days.

No mortality or significant signs of toxicity were observed during the study period, indicating that both HENI and HENI-loaded phytosomes were safe at the tested dose.

Experimental Animals

Healthy adult Wistar albino rats of either sex weighing between 150 and 200 g were procured from the institutional animal facility. Animals were housed in polypropylene cages under standard laboratory conditions maintained at 25 ± 2°C with relative humidity of 55–65% and a 12-hour light/dark cycle.

Standard pellet diet and filtered drinking water were provided ad libitum throughout the experimental period. Animals were acclimatized for one week before initiation of the experiment. All experimental procedures were performed during daytime between 08:00 and 15:00 h to minimize circadian variation.

The experimental protocol complied with CPCSEA guidelines for laboratory animal care and use.

Induction of Experimental Type 2 Diabetes

Experimental type 2 diabetes mellitus was induced using the streptozotocin–nicotinamide model described by Fischer et al. (1998). Following overnight fasting, rats received nicotinamide (120 mg/kg, intraperitoneally). Fifteen minutes later, streptozotocin (60 mg/kg, intraperitoneally), freshly prepared in cold citrate buffer (0.1 M, pH 4.5), was administered.

Blood glucose concentrations were determined after 72 hours and again on the seventh day using blood collected from the tail vein. Animals exhibiting fasting blood glucose levels greater than 126 mg/dL were considered diabetic and included in the experimental study.

Experimental Design

Forty-two diabetic rats were randomly divided into seven experimental groups containing six animals each.

Group I: Normal control (drinking water)

Group II: Diabetic control

Group III: Glibenclamide (0.5 mg/kg)

Group IV: HENI (100 mg/kg)

Group V: HENI (200 mg/kg)

Group VI: HENI-loaded phytosomes (100 mg/kg)

Group VII: HENI-loaded phytosomes (200 mg/kg)

All treatments were administered orally once daily for 21 consecutive days.

Determination of Blood Glucose Level

Fasting blood glucose was measured on Day 1, Day 7, and Day 21 using blood collected from the tail vein. Blood glucose concentrations were determined using a digital glucometer and expressed as mg/dL.

Measurement of Body Weight

Body weights of all experimental animals were recorded before induction of diabetes and at the end of the treatment period. The percentage change in body weight was calculated to evaluate the protective effect of treatments against diabetes-associated weight loss.

Estimation of Biochemical Parameters

At the completion of the experimental period, animals were euthanized by cervical dislocation following overnight fasting. Blood samples were collected by cardiac puncture and centrifuged at 3000 rpm for 15 minutes to separate serum.

The following biochemical parameters were determined using commercially available diagnostic kits and an automated biochemical analyzer:

- Total cholesterol
- Triglycerides
- High-density lipoprotein (HDL)
- Low-density lipoprotein (LDL)
- Total protein
- Serum glutamate pyruvate transaminase (SGPT)
- Serum glutamate oxaloacetate transaminase (SGOT)
- Serum alkaline phosphatase (SALP)

These biomarkers were selected to evaluate lipid metabolism, hepatic function, and systemic metabolic alterations associated with diabetes.

Stability Study of Optimized HENI-Loaded Phytosomes

The optimized phytosomal formulation was subjected to stability studies according to ICH Q1A(R2) recommendations.

Samples were stored under the following conditions:

- Accelerated condition: 40 ± 2°C / 75 ± 5% RH
- Room temperature: 25 ± 2°C / 60 ± 5% RH

The stability study was continued for three months.

Samples were analyzed at 0, 1, 2, and 3 months for:

- Physical appearance
- Colour
- Particle size
- Entrapment efficiency
- In vitro drug release

The obtained results were compared with the initial formulation to evaluate physicochemical stability.

Statistical Analysis

Experimental data were expressed as Mean ± Standard Error of Mean (SEM) for pharmacological studies and Mean ± Standard Deviation (SD) for physicochemical evaluations. Statistical analysis was performed using one-way

analysis of variance (ANOVA) followed by an appropriate post hoc multiple comparison test. A value of **p < 0.05** was considered statistically significant.

Results and Discussion

Pharmacological activity

Up to the highest dose of 2000 mg/kg body weight, it must have been discovered that simple HENI and HENI loaded phytosomes were not toxic.

Table 3.1: Antidiabetic effect of simple HENI and HENI loaded phytosomes in STZ treated rodents

Group	Treatment	Serum glucose levels (mg/dl)		
		1st Day	7th Day	21st Day
I	Normal Control	75.25 ± 4.18	95.30 ± 5.20	111.10 ± 6.22
II	Diabetic Control	296.15 ± 5.40	383.23 ± 6.05#	410.12 ± 8.35[a]
III	Diabetic + Glibenclamide	264.73 ± 6.55	132.10 ± 6.30*	92.34 ± 6.41*
IV	Diabetic + HENI (100 mg/kg)	269.12 ± 5.36	146.20 ± 4.74	137.20 ± 7.14*
V	Diabetic + HENI (200 mg/kg)	264.03 ± 4.29	141.10 ± 7.90*	119.16 ± 5.23*
VI	Diabetic + HENI loaded Phytosomes (100 mg/kg)	274.50 ± 6.87	136.00± 7.61	122.52 ± 6.19*
VII	Diabetic + HENI loaded Phytosomes (200 mg/kg)	269.40± 6.32	133.10 ± 5.25*	96.18 ± 4.72*

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at [a]P<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

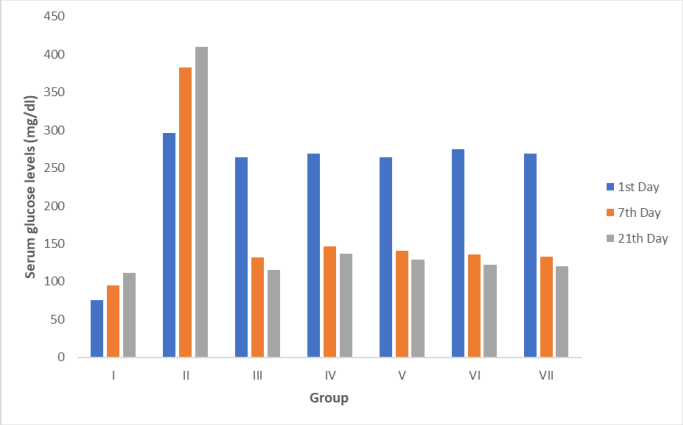

Fig 3.1: Antidiabetic effect of simple HENI and HENI loaded phytosomes in STZ treated rodents

Table 3.2: Efficacy of simple HENI and HENI loaded phytosomes on body weight in rats

Group	Treatment	Body Weight (gm)	
		Initial weight (g)	Final weight (g)
I	Normal Control	194.11 ± 7.65	211.13 ± 9.24
II	Diabetic Control	202.15 ± 6.58	169.74 ± 7.82[a]
III	Diabetic + Glibenclamide	193.06 ± 8.32	211.15 ± 5.62*
IV	Diabetic + HENI (100 mg/kg)	181.16 ± 4.92	192.37 ± 8.41*
V	Diabetic + HENI (200 mg/kg)	171.56 ± 6.81	204.25 ± 5.26*
VI	Diabetic + HENI loaded Phytosomes (100 mg/kg)	164.13 ± 5.10	187.19 ± 6.49*
VII	Diabetic + HENI loaded Phytosomes (200 mg/kg)	166.38 ± 6.72	202.53± 4.11*

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at [a]P<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

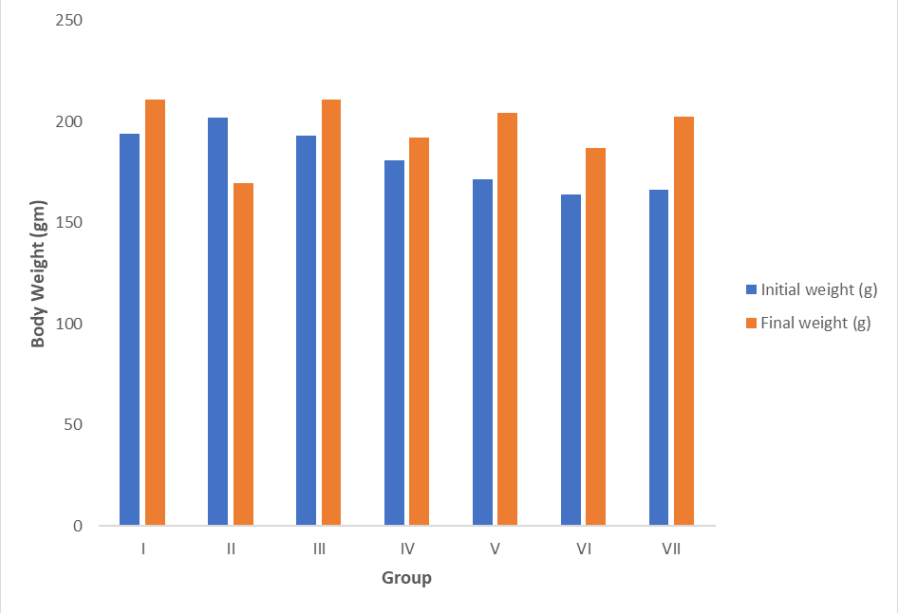

Fig 3.2: Efficacy of simple HENI and HENI loaded phytosomes on body weight in rats

Table 3.3: Efficacy of simple HENI and HENI loaded phytosomes on total cholesterol level in experimental animals

Group	Treatment	Total Cholesterol (mg/dl)
I	Normal Control	145. 95±4.82
II	Diabetic Control	254.62±9.14[a]
III	Diabetic + Glibenclamide	193.12±5.51*
IV	Diabetic + HENI (100 mg/kg)	208.91±8.12*
V	Diabetic + HENI (200 mg/kg)	202.50±9.96*
VI	Diabetic + HENI loaded Phytosomes (100 mg/kg)	203.72±8.52*

VII	Diabetic + HENI loaded Phytosomes (200 mg/kg)	197.08±9.13*

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at [a]P<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

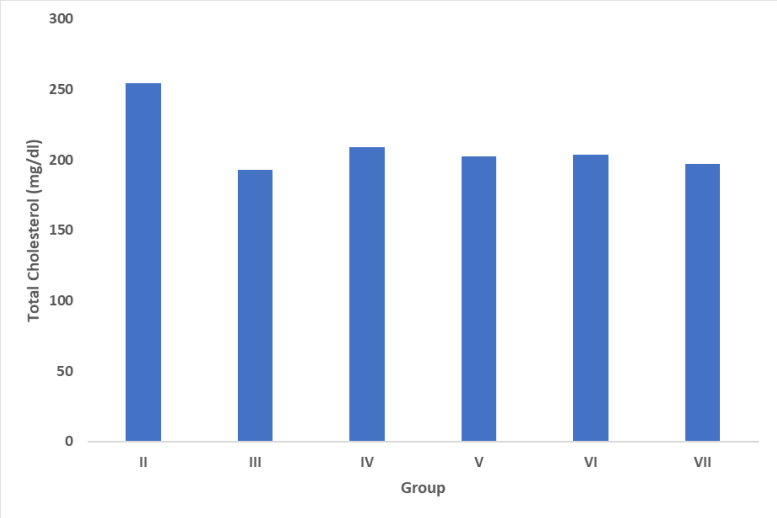

Fig 3.3: Efficacy of simple HENI and HENI loaded phytosomes on total cholesterol level in experimental animals

Table 3.4: Efficacy of simple HENI and HENI loaded phytosomes on triglyceride level in experimental animals

Group	Treatment	Triglyceride (mg/dl)
I	Normal Control	116.10±4.13
II	Diabetic Control	217.35±4.67[a]
III	Diabetic + Glibenclamide	134.72±5.25*
IV	Diabetic + HENI (100 mg/kg)	172.58±4.85*
V	Diabetic + HENI (200 mg/kg)	164.35±4.59*
VI	Diabetic + HENI loaded Phytosomes (100 mg/kg)	156.67±4.49*
VII	Diabetic + HENI loaded Phytosomes (200 mg/kg)	154.14±4.62*

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at [a]P<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

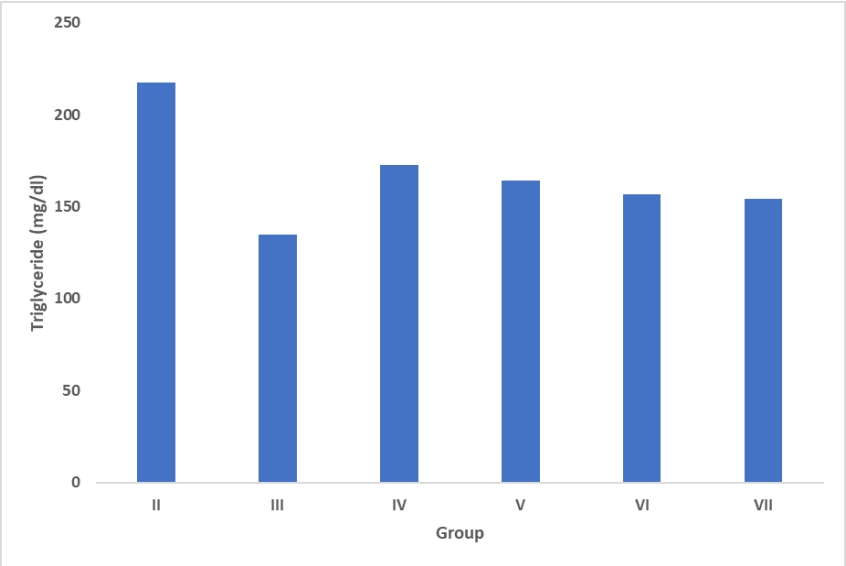

Fig 3.4: Efficacy of simple HENI and HENI loaded phytosomes on triglyceride level in experimental animals

Table 3.5: Efficacy of simple HENI and HENI loaded phytosomes on HDL level in experimental animals

Group	Treatment	HDL (mg/dl)
I	Normal Control	51.52±2.48
II	Diabetic Control	31.14±1.55[a]
III	Diabetic + Glibenclamide	49.95±1.63[*]
IV	Diabetic + *HENI* (100 mg/kg)	44.55±1.75[*]
V	Diabetic + *HENI* (200 mg/kg)	45.39±1.82[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	46.45±1.57[*]
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	47.50±1.28[*]

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

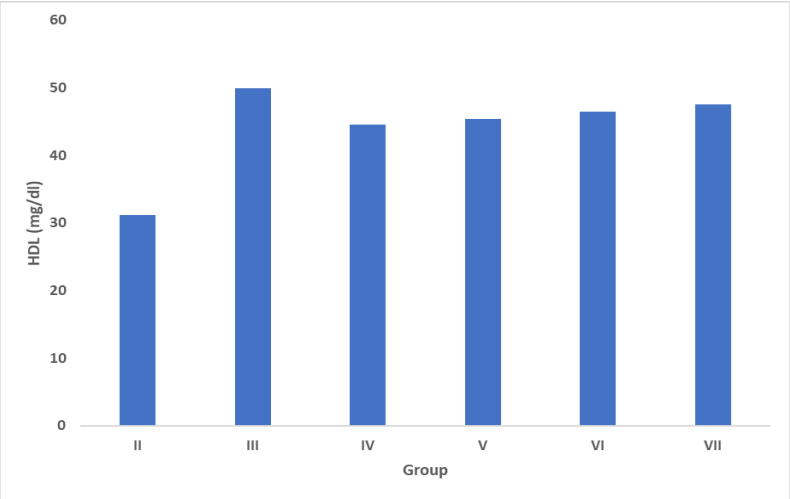

Fig 3.5: Efficacy of simple HENI and HENI loaded phytosomes on HDL level in experimental animals

Table 3.6: Efficacy of simple HENI and HENI loaded phytosomes on LDL level in experimental animals

Group	Treatment	LDL (mg/dl)
I	Normal Control	79.63±6.81
II	Diabetic Control	183.18±5.99[a]
III	Diabetic + Glibenclamide	91.25±5.94[*]
IV	Diabetic + *HENI* (100 mg/kg)	125.34±6.17[*]
V	Diabetic + *HENI* (200 mg/kg)	121.50±5.87[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	119.24±5.82[*]
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	109.44±5.32[*]

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

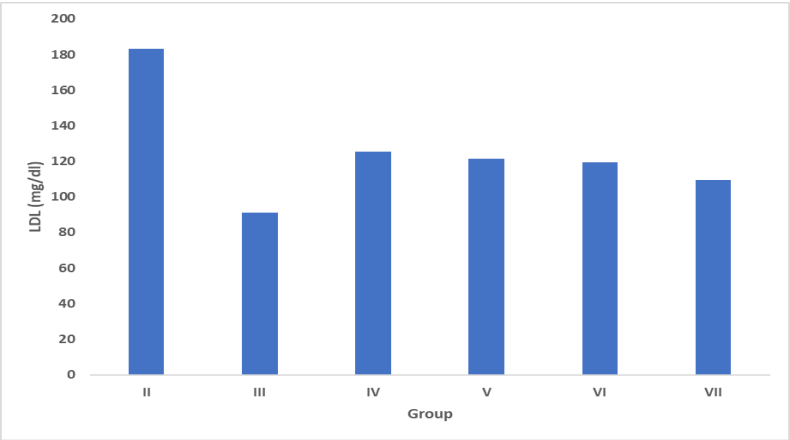

Fig 3.6: Efficacy of simple HENI and HENI loaded phytosomes on LDL level in experimental animals

Table 4.25: Efficacy of simple HENI and HENI loaded phytosomes on total protein in experimental animals

Group	Treatment	Total Protein (g/dl)
I	Normal Control	7.91 ± 6.28
II	Diabetic Control	19.42± 4.17[a]
III	Diabetic + Glibenclamide	8.36 ± 3.12*
IV	Diabetic + *HENI* (100 mg/kg)	8.62 ± 3.78*
V	Diabetic + *HENI* (200 mg/kg)	8.51 ± 7.19[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	8.48 ± 3.41*
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	8.11 ± 2.79*

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

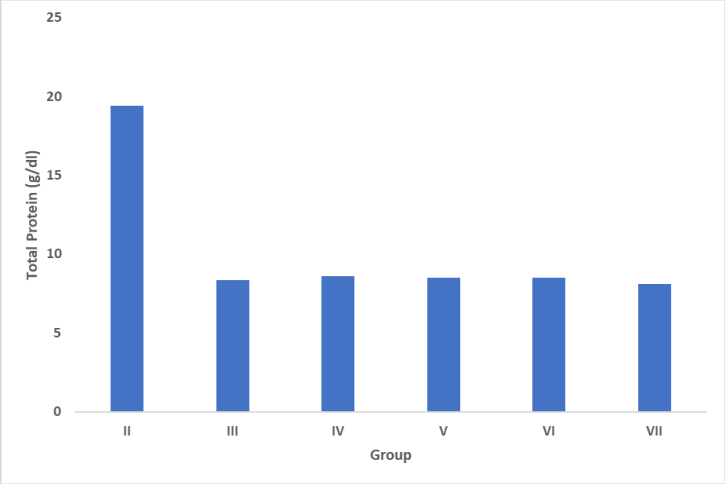

Fig3.6: Efficacy of simple HENI and HENI loaded phytosomes on total protein in experimental animals

Table 3.7: Efficacy of simple HENI and HENI loaded phytosomes on SGPT in experimental animals

Group	Treatment	SGPT (U/L)
I	Normal Control	59.23±3.61
II	Diabetic Control	138.26±4.32[a]
III	Diabetic + Glibenclamide	81.15±6.89[*]
IV	Diabetic + *HENI* (100 mg/kg)	107.02±5.75[*]
V	Diabetic + *HENI* (200 mg/kg)	103.16±3.82[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	92.51±4.13[*]
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	87.19±3.27[*]

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

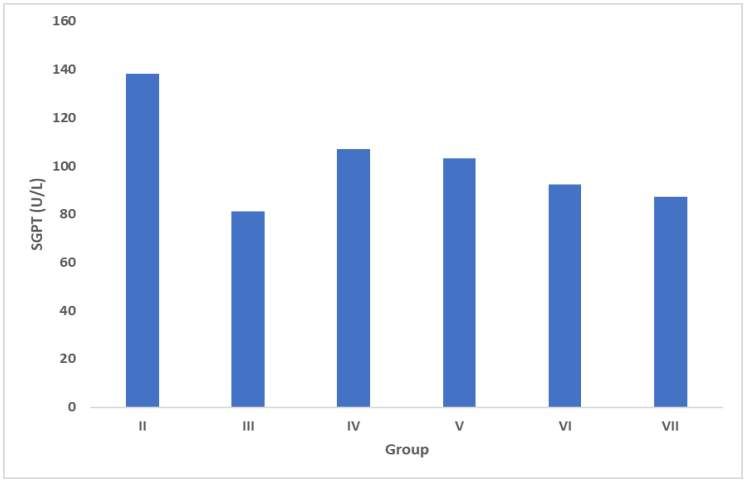

Fig 3.7: Efficacy of simple HENI and HENI loaded phytosomes on SGPT in experimental animals

Table 3.8: Efficacy of simple HENI and HENI loaded phytosomes on SGOT in experimental animals

Group	Treatment	SGOT (U/L)
I	Normal Control	44.81±3.62
II	Diabetic Control	137.17±5.08[a]
III	Diabetic + Glibenclamide	61.24±3.19[*]
IV	Diabetic + *HENI* (100 mg/kg)	90.98±2.57[*]
V	Diabetic + *HENI* (200 mg/kg)	88.98±4.23[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	81.05±3.67[*]
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	74.27±2.51[*]

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

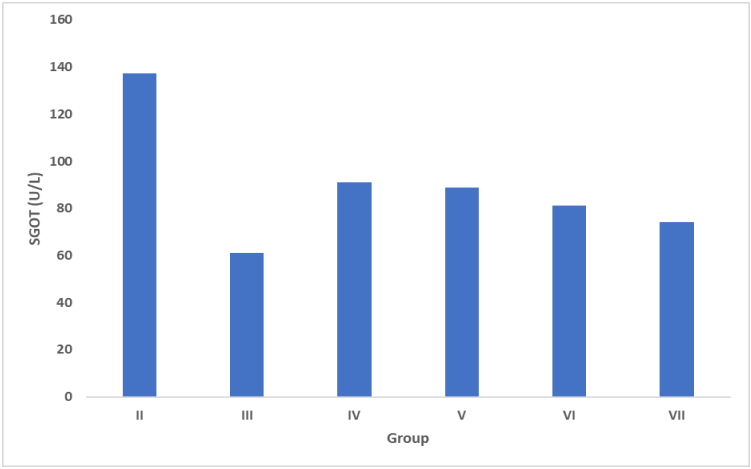

Fig 3.8: Efficacy of simple HENI and HENI loaded phytosomes on SGOT in experimental animals

Table 3.9: Efficacy of simple HENI and HENI loaded phytosomes on SALP in experimental animals

Group	Treatment	SALP (U/L)
I	Normal Control	146.21±3.16
II	Diabetic Control	301.91±4.20[a]
III	Diabetic + Glibenclamide	170.26±5.14[*]
IV	Diabetic + *HENI* (100 mg/kg)	204.29±3.02[*]
V	Diabetic + *HENI* (200 mg/kg)	190.99±4.37[*]
VI	Diabetic + *HENI* loaded Phytosomes (100 mg/kg)	189.75±5.82[*]
VII	Diabetic + *HENI* loaded Phytosomes (200 mg/kg)	184.60±2.31[*]

Findings are demonstrated in the form of mean ± SEM (n=6); indicating significant statistically difference at aP<0.05 once comparing to the normal group, and *P<0.05 once comparing to the diabetes group

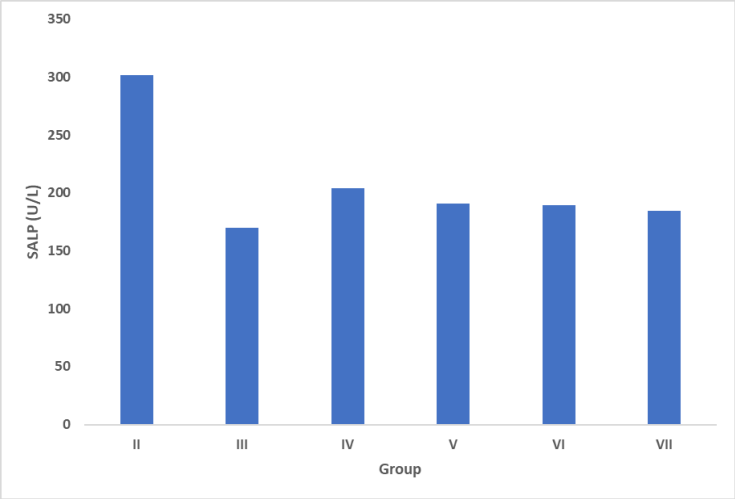

Fig 3.9: Efficacy of simple HENI and HENI loaded phytosomes on SALP in experimental animals

Stability studies

Table 3.10: Any alteration in Colour of HENI loaded phytosomes at accelerated condition

Studied	Remark	Results
Description	No changed of color	Complies with the stability condition

Table 3.10: Comparison of physicochemical data of HENI loaded phytosomes at accelerated temperature condition (400C ± 20C / 75% RH ± 5%)

Months	Particle size (nm)	Entrapment efficiency (%)
0	177.2 ± 1.27	72.53 ± 3.41
1	178.5 ± 2.15	71.61 ± 4.13
2	178.9 ± 1.84	71.34 ± 2.51

3	180.3 ± 1.62	70.13 ± 2.73

Values are mean ± S.D

Table 3.11: Comparison of dissolution data of HENI loaded phytosomes at accelerated condition (400C ± 20C / 75% RH ± 5%)

Time (hrs)	Initial (0 days)	30 days	60 days	90 days
1	19.23±0.76	20.16±0.84	19.82±0.49	21.42±0.52
2	29.45±0.82	29.46±0.37	28.17±0.53	30.19±0.93
4	42.15±0.19	41.39±0.28	41.75±0.25	42.28±0.45
6	57.34±0.52	58.62±0.19	58.29±0.67	57.63±0.28
8	68.72±0.61	68.52±0.73	68.84±0.39	69.08±0.57
10	80.14±0.46	82.58±0.52	81.17±0.41	82.41±0.41
12	94.05±0.32	93.16±0.76	93.68±0.86	94.25±0.73

Values are mean ± S.D

Table 3.12: Any alteration in Colour of HENI loaded phytosomes at room temperature

Studied	Remark	Results
Description	No changed of color	Complies with the stability condition

Table 3.13: Comparison of physicochemical data of HENI loaded phytosomes at room temperature (250C ± 20C / 60% RH ± 5%)

Months	Particle size (nm)	Entrapment efficiency (%)
0	177.4 ± 2.35	72.69 ± 1.57
1	178.2 ± 3.64	71.82 ± 2.43
2	178.3 ± 2.51	71.14 ± 1.72
3	180.6 ± 3.75	70.02 ± 1.26

Values are mean ± S.D

Table 3.14: Comparison of dissolution data of HENI loaded phytosomes at room temperature (250C ± 20C / 60% RH ± 5%)

Time (hrs)	Initial (0 days)	30 days	60 days	90 days
1	20.15±0.43	19.42±0.53	21.73±0.68	19.28±0.27
2	29.46±0.72	28.37±0.48	29.82±0.41	29.42±0.58
4	41.73±0.18	42.58±0.62	41.61±0.86	41.65±0.36
6	58.36±0.39	57.16±0.93	59.73±0.57	58.27±0.79
8	67.13±0.25	69.32±0.81	69.15±0.39	68.71±0.61
10	81.69±0.76	82.49±0.37	82.26±0.42	81.32±0.59
12	93.17±0.19	94.64±0.24	93.11±0.55	94.85±0.43

Values are mean ± S.D

Conclusion

The present study demonstrated that the hydroalcoholic extract of Niruris indica (HENI) possesses significant antidiabetic activity in streptozotocin–nicotinamide-induced diabetic rats. Oral administration of HENI significantly reduced fasting blood glucose levels, improved body weight, corrected dyslipidemia, and restored altered hepatic biochemical markers compared with the diabetic control group. The HENI-loaded phytosomal formulation exhibited superior therapeutic efficacy over the plain hydroalcoholic extract at equivalent doses, indicating that phytosome technology effectively enhanced the oral bioavailability and pharmacological activity of the plant extract. Acute oral toxicity studies confirmed the safety of both HENI and HENI-loaded phytosomes up to a dose of 2000 mg/kg. Furthermore, the optimized phytosomal formulation remained physically and chemically stable under both accelerated and room-temperature storage conditions for three months, with minimal changes in particle size, entrapment efficiency, and drug release characteristics. Overall, the findings suggest that HENI-loaded phytosomes represent a promising herbal nanocarrier system for improving the therapeutic management of diabetes mellitus and warrant further pharmacokinetic, mechanistic, and clinical investigations.

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