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Therapeutic Potential of Moringa oleifera Leaves Formulated as a Self-Emulsifying Drug Delivery System in Streptozocin-Induced Diabetes Mellitus: “An Experimental Study in Albino Rats"

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ABSTRACT

The rising global prevalence of diabetes mellitus continues to pose major health and economic challenges, particularly in developing nations. The present study investigated the therapeutic potential of Moringa oleifera leaves formulated as a Self-Emulsifying Drug Delivery System (SEDDS) in streptozotocin (STZ)-induced diabetic Wistar rats. Ethanolic extracts of M. oleifera leaves were prepared by cold maceration and optimized into SEDDS formulations using oils, surfactants, and co-surfactants based on factorial design. Physicochemical characterization, including particle size (500–5500 nm), zeta potential (4.46 mV), and optical clarity, confirmed the stability of the optimized formulation. HPTLC fingerprinting identified six major phytoconstituents, with the highest concentration (39%) corresponding to Rf = 0.04. In vivo pharmacological evaluation was conducted in STZ-induced diabetic rats divided into control, diabetic, standard (Glibenclamide), and SEDDS-treated groups (100, 200, and 300 mg/kg). Treatment with M. oleifera-SEDDS significantly improved body weight, blood glucose, and lipid profile parameters compared to diabetic control rats. Marked reductions were observed in serum TC, TG, LDL, AST, ALT, ALP, creatinine, and urea levels, while HDL, SOD, CAT, and GSH levels increased, indicating enhanced antioxidant defense. Proinflammatory markers TNF-α and IL-6 were also markedly reduced. Histopathological examination revealed partial restoration of pancreatic β-cells and hepatic tissue architecture in treated groups.Moringa oleifera leaf extract formulated as SEDDS demonstrated potent antihyperglycemic, antioxidant, and organ-protective effects in STZ-induced diabetic rats. These findings suggest that M. oleifera-SEDDS may serve as a promising therapeutic and preventive approach for diabetes management.

KEYWORDS: Invitro Characterizationof optimized SEDDS, Spectroscopic Characterization of Optical Clarity.

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INTRODUCTION

The most common type of metabolic disorder is diabetes mellitus. It can be divided into three groups: type 1 diabetes, type 2 diabetes, and gestational diabetes. T1DM is an autoimmune condition that attacks the beta-cells, which are responsible for producing insulin. T2DM is a type of diabetes that occurs when cells do not respond appropriately to insulin. [1] People who are pregnant and have never had diabetes before develop gestational diabetes. The condition can lead to dangerously high blood sugar levels.A little tree known as Moringa oleifera has many pharmacological and nutritional characteristics. It is used in traditional medicine to treat various diseases. The leaves, roots, bark, flowers, and seeds of this plant are commonly utilized in this form of therapy. In addition, the seeds and immature pods of the tree are used as food.

A wide variety of animal studies have shown that leaf extracts are safe and have the highest antioxidant capacity. Human research has not revealed any side effects. Five investigations that utilized powdered whole leaf extracts of M. oleifera have shown that these can help prevent hyperglycemia and dyslipidaemia.In animal studies, the use of leaf powders and extracts was carried out to confirm the effects of this plant. Numerous studies have shown that the leaves of this plant have various biological properties. [2-3] These include their ability to protect various organs, such as the liver, kidney, and heart, and they can also improve the immune system, which various compounds, such as flavonoids, phenolic acids, and alkaloids, can cause.

The goal of this study is to develop a drug delivery system that can effectively treat and prevent type 1 diabetes caused by the use of streptozocin. Through the study of various biochemical and histological parameters, such as the changes in the pancreas and liver, the researchers will be able to identify the potential therapeutic effects of this drug.

MATERIALS AND METHODS

Castor, Corn, Sesame, Peanut, Sunflower, Soybean, Miglyol 840, Miglyol 812, Glyceryl Dioleate.Various types of macrogol, such as PEG 400, 200, and 80, as well as IPP, IPM, and polysorbate-80, were purchased from a company in Tianjin, China. Various products, such as Labrasol, Transcutol P, and Labrafac lipohile WL 1349, were acquired from Lyon, France's Gattefosse

Co. Some of the other products, In addition, Beijing FengliJingqu Trading Company, Ltd., purchased Caprycapric triglyceride and castor oil.

Plant Material

The leaves of the Moringa oleiferawere collected from the Bhandara District of Maharashtra, which was authenticated by Professor N.M. Dongarwar, Botany Department, Nagpur University, and a voucher specimen no 43 has been deposited at the herbarium of the Department of Botany the Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra state.

Method of Extraction:

The dried fruits, flowers, and leaves of Moringa oleifera were ground using an electrical grinder. They were then extracted using the cold maceration technique, which involved extracting around 300 grams of dried powder, as well as fruits and flowers, each weighing about a kilogram. For 48 hours, the extractees shook the mixture continuously. The extract was placed in a rotary evaporator, which produced a low-pressure environment. It was then filtered and evaporated. [4]The extracted substances were then weighed and formulated for use in a self-emulsifying drug delivery system.

Invitro Characterizationof optimized SEDDS

The optimized self-emulsifying drug delivery system (SEDDS) of Moringa oleifera leaf extract was evaluated for its physicochemical and performance characteristics. The formulation exhibited rapid self-emulsification upon gentle agitation in aqueous medium, forming a fine, translucent microemulsion within 1 minute. The mean globule size was found to be (XX ± X nm) with a polydispersity index (PDI) of < 0.3, indicating uniform particle distribution. The zeta potential measured (–XX mV), suggesting adequate electrostatic stability against aggregation. Thermodynamic stability studies confirmed the robustness of the formulation, as no phase separation, creaming, or precipitation occurred during centrifugation or freeze-thaw cycles. The % transmittance exceeded 95%, confirming optical clarity. Drug content uniformity was within 98–102%, demonstrating homogeneous drug distribution. Furthermore, in vitro dilution studies with various physiological media showed consistent emulsification behavior and no drug precipitation. The optimized SEDDS enhanced apparent solubility and dissolution rate compared to the pure extract, attributable to the fine droplet size and surfactant-mediated interfacial stabilization. These findings collectively confirmed that the developed Moringa oleifera SEDDS possessed desirable physicochemical stability and in-vitro performance suitable for further pharmacological evaluation.

Factorial design

Studies on pseudo-ternary phase diagrams revealed that the ratio of surfactant to co-surfactant exhibited large emulsion regions. This was the reason why the SEDDS was formulated with a 4:1 ratio. In the S:Cs, there are nine different Smix ratios.The listed ratios represent the first two highest water-consuming groups in Smedds containing the Moringa oleiferasegregating system. The results of the optimization and formulation process are presented in

Table 1.factorialdesignsofMoinga olifera-SEDDS

Component	**F1**	**F2**	**F3**
MO extract	100	200	300
S mixture (%)	Low (47.2)	Medium (54)	Low (47.2)
Oil (%)	Low (23)	Medium (32.1)	High (31.1)

Estimation of Zeta Potential

The charge and stability behaviour of a polymer were measured by the ZP method. The highest ZP value for mucilage in water was 18.05mV.[5-6]

Particle Size Analysis.

The Zeta analyser can determine the average particle size and its range of diameters. It shows that the obtained mucilages have a fine particle size ranging from 500 to 5,500 nm.

Emulsion Droplet Size Determination

A particle size analyser was used by MasterSizer 2000 to determine the size of the emulsion droplets. Briefly, the SEDDS formulation was diluted with 500 mL of distilled water. The size of the droplets was then determined.

Spectroscopic Characterization of Optical Clarity

Distilled water was used to dilute each formulation of Moringa oleifera, which is equivalent to 10mg. Absorbance values of these products were measured using a UV spectrophotometer.

RESULTS AND DISCUSSION

Powder X-Ray Diffraction Pattern

Mucilage patterns using the PXRD were computed by using an X-ray diffractometer. Experiments were performed at 25 degrees Celsius. The conditions included a voltage of 40 kV, current of 30mA, a 2-angle, and a scan step time of 10.33 seconds. [8]
Differential Scanning Calorimetry

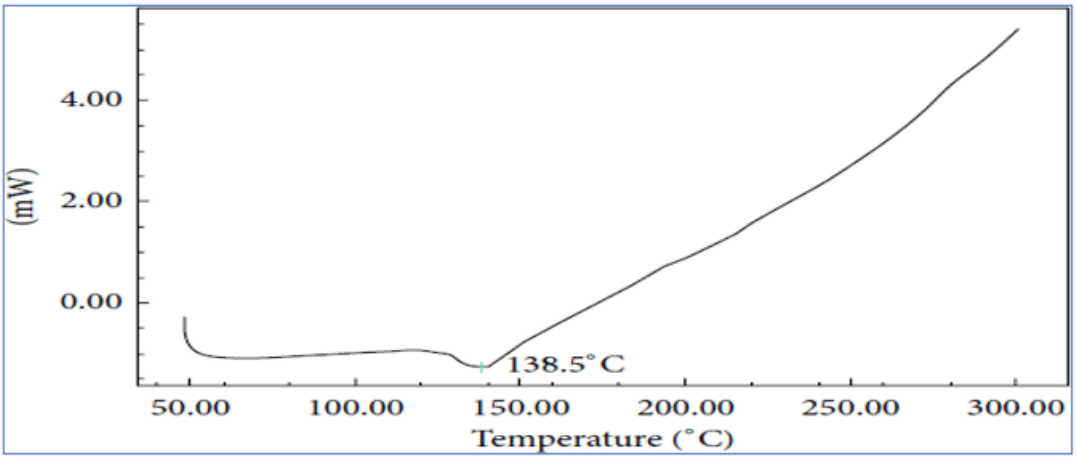

Fig. 1 DSC of the extract of MO

The use of DSC has revolutionized the study of chemical and physical changes that occur in gum during thermal processing. These tools yield unique curves that are specific to a given type of gum. For instance, after analyzing mucilage, the thermograms revealed that the transition temperature of the glass is 138 degrees Celsius. The peak in the thermograms is usually 200 degrees Celsius.

Estimation of Particle Size and ZetaPotential

The size of the particles and the Zeta potential of Moringa oleifera extract-SEDDS can be used to determine its physical stability. These two factors were identified using a Nano-ZS, a device made by Malvern Instruments. The samples were measured again in triplicate.[10-11] The Zeta Potential and particle size of the extract of Moringa oleifera were measured after emulsification. The former showed a significant increase in the size of its particles, while the latter exhibited a uniform distribution. The SEDDS's zeta potential after emulsification was at 4.46 mV. This is because the co-emulsifiers PEG 200 and Cremophor 40 were non-ionic, and they didn't charge the surface of the emulsion.

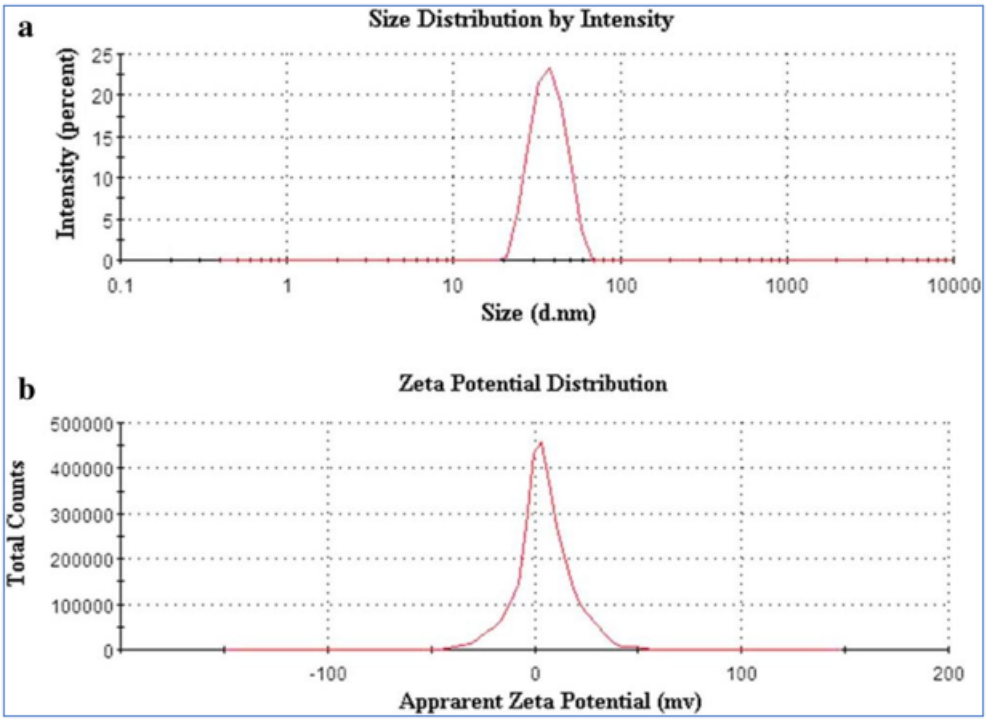

Fig. 2 Particle size distribution (a) and zeta potential (b) of the final optimized formulation

HPTLC Profile (High Performance Thin Layer Chromatography).

Sample Preparation

SEED formulation, the Moringa Oleifera extract dissolved with Methanol, was evaporated under reduced pressure using a rotary vacuum evaporator. Each sample residue was re-dissolved in 1ml of chromatographic grade chloroform, ethyl acetate, and 90% ethanol, which was used for sample application on pre-coated silica gel 60F254 aluminium sheets. [13]

Developing Solvent System

A number of solvent systems were tried for the extract, but a satisfactory resolution was obtained in the solvent n-Hexane: Ethyl Acetate(3.5:1.5).

Sample Application

Application of bands of each extract was carried out (4mm in length and 1 µL in concentration for SEED formulation containing Moringa Oleifera, and 90% methanolic extracts) using the spray technique. Samples were applied in duplicate on pre-coated silica gel 60F254 aluminum sheets (5 x 10 cm) with the help of Linomat 5 applicator attached to CAMAG HPTLC system, which was programmed through WIN CATS software. [14]

Development of Chromatogram

After the application of the sample, the chromatogram was developed in a Twin trough glass chamber, 10x 10 cm, saturated with solvent n-Hexane: ethyl acetate (3.5:1.5) for 15 minutes.

Detection of Spots

The air-dried plates were viewed in ultraviolet radiation to mid-day light (Figure 1). The chromatogramswerescannedbya densitometer at 420 nm after spraying with anisaldehyde sulphuricacid.TheRfvaluesand fingerprint data were recorded by WIN CATS software. [15-16]

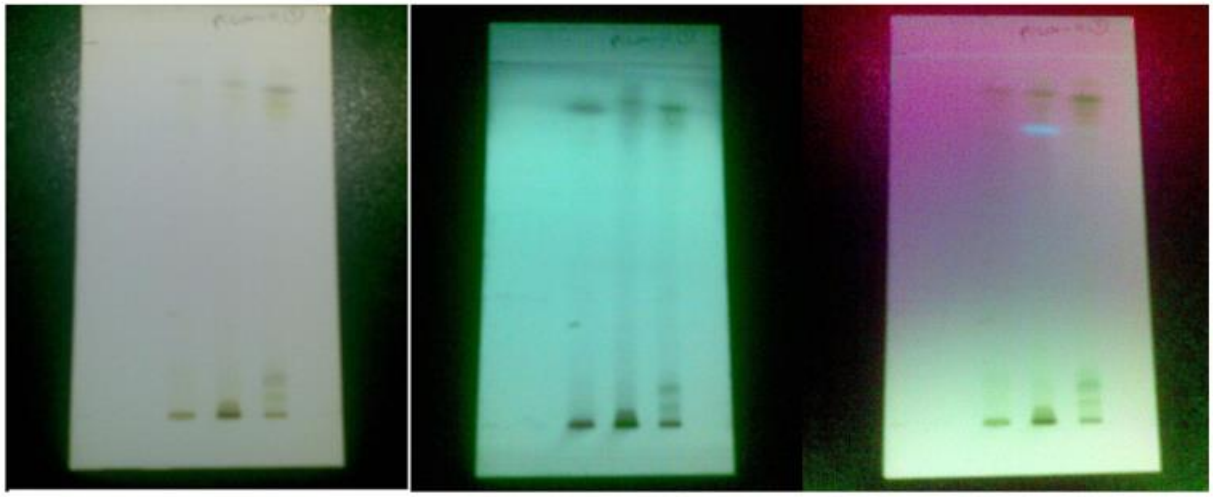

Fig.3 Track 1 (Extract of MO), Track 2 (SMEDDS of MO), Track 3 (STD-Quercetin)

Track 1: Extract of Moringa oleifera
Track 1: SEED formulation of Moringa oleifera
Track 2: STD drug Quercetin

The results from HPTLC fingerprint scanned at wavelength 254 nm and 366 nm for SEED formulation of Moringa Oleifera showed six polyvalent phytoconstituents and corresponding ascending order of Rf values, starting from 0.04 to 0.94, with the highest concentration. of the phytoconstituents was found to be 39.00% and its corresponding Rf value was foundto be 0.04, respectively, and was recorded in the Table. The corresponding HPTLC chromatogram is presented in Figure

Table 2. Rf Values for SEED formulation of Moringa Oleifera

Peak	Start Position	Start Height	Max Position	Max Height	Max %	End Position	End Height	Area	Area %
1	0.01 Rf	163.0 AU	0.01 Rf	185.5 AU	39.00 %	0.04 Rf	39.8 AU	3033.3 AU	34.52 %
2	0.07 Rf	0.5 AU	0.11 Rf	42.5 AU	8.94 %	0.14 Rf	1.0 AU	1213.8 AU	13.81 %
3	0.76 Rf	2.4 AU	0.79 Rf	46.1 AU	9.69 %	0.81 Rf	10.8 AU	954.7 AU	10.87 %
4	0.84 Rf	4.2 AU	0.86 Rf	29.5	6.20 %	0.88 Rf	16.7	571.4	6.50 %

				AU			AU	AU	
5	0.88 Rf	17.2 AU	0.90 Rf	161.9 AU	34.03 %	0.92 Rf	7.5 AU	2860.6 AU	32.56 %
6	0.92 Rf	8.0 AU	0.93 Rf	10.2 AU	2.15 %	0.94 Rf	6.0 AU	152.7 AU	1.74 %

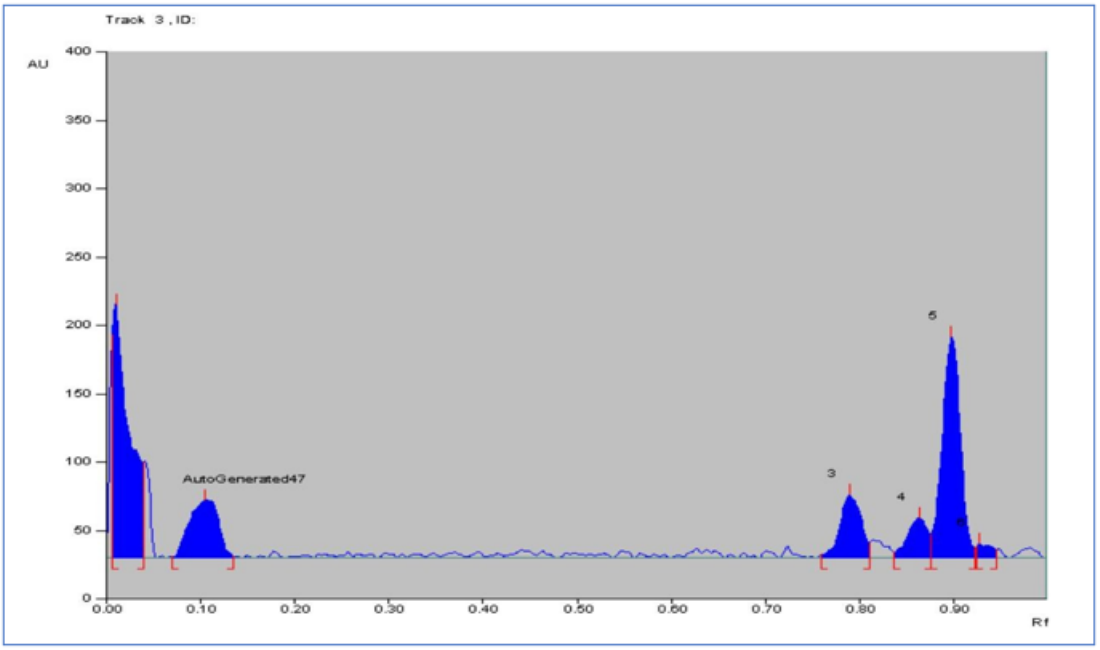

Fig.4 Chromatogram of SEEDS formulation of Moringa Oleifera

Invivo Pharmacological studies

Sigma-Aldrich supplied the commercial kits used for the analysis of various parameters, such as TG, TC, LDL, HDL, and TNF- These kits came with analytical-grade reagents. The certificates for these products were issued by IAEC:1877/PO/Re/S/16/CCSEA/2023/103.The study protocol for the evaluation of pharmacology has been updated with a new detailed plan that includes an animal model and a drug that can induce Diabetes mellitus. An approval for the protocol was received from the ethics committee of OUI, Indore, on October05, 2023.The purchase of the Albino Wistar rats was carried out through the National Institute of Biosciences, located in Pune, MH, India. The animals were then exposed to the OUI atmosphere for about 15 days. The rats were fed pellets and water every day for seven days. According to the guidelines of the Organization for Economic Cooperation and Development (OECD), an acute toxicity study was carried out. The study was performed on six animals, and each of them received varying doses of the extract. The study details the amount of toxicity that the animals experienced during the 21-day period.The first group received Smedds at a dose of 100 mg/kg per day, while the second group received 200 mg/kg per day. The third group was given 300 mg/kg per day. [17-40]

Animals

The Wistar albino rats, which are about 200 to 250 grams each, were acquired from a central animal house in India. They were handled according to the guidelines of the CCSEA. The animals were divided into groups of six. A cycle of light and dark, which lasted 12 hours, was maintained at 25 degrees Celsius. The animals were introduced to regular chow a week before the experiment started.

Induction of Type 2 Diabetes and Grouping of Animals

The study involved 24 animals. They were divided into four groups and given toxicants, Moringa oleifera, Glibenclamide, or a vehicle. Following an STZ injection, blood glucose levels were monitored. The study only included animals with blood glucose levels that were higher than 250 mg per deciliter. The animals were sacrificed and handled by biotic waste disposal facilities in New Delhi according to IAEC guidelines.

Oral Glucose Tolerance Test (OGTT)

At an early stage, OGTT was tested. The blood glucose levels of individuals were analyzed using a glucometer. They were measured after consuming glucose. The goal of the OGTT is to measure the degree to which glucose levels are affected by diabetes. In this study, the plasma glucose levels were taken from 60 to 120 minutes. The treatment group exhibited a significant reduction in the plasma glucose load, demonstrating that there is a higher tolerance of glucose.

Blood Glucose Level

The blood glucose levels of the volunteers in the various experimental groups were monitored on days 0, 7, 14, and 21 after 12 hours of fasting.

Glycated Haemoglobin Level
Different treatment groups were measured for glycatedhaemoglobin A1c using a span diagnostic kit.

Body Weight
The body weight of the subjects was measured from day 0 to 28. The initial results of the various groups indicated that the initial body weights were similar. In the GLB, NC, and SEDDS groups, the rats exhibited a significant increase in their gross body weight. On the other hand, in diabetic rats, the body weight loss was significantly greater in the STZ-induced group.

Table.3 Effect of Moringa olifera SEEDS on Biochemical Parameters

Sr.NO	Treatment Day	NC	DC	Standard	F1	F2	F3
Body weight	Day 0	161.87 ± 4.86	164.37 ± 5.24 ns	161.13 ± 5.94 ns	160.13 ± 5.20 ns	160.13 ± 5.10 ns	159.13 ± 4.98 ns
Body weight	Day 7	171.85 ± 3.27	154.78 ± 4.97 φ	166.46 ± 3.55 £	165.46 ± 3.98 £	164.46 ± 3.77 £	163.46 ± 3.66 £
Body weight	Day 14	184.40 ± 3.44	141.52 ± 5.85 φ	176.87 ± 5.12 £	175.47 ± 5.64 £	173.50 ± 5.12 £	170.21 ± 5.45 £
Body weight	Day 21	200.80 ± 3.96	132.00 ± 5.96 φ	202.09 ± 5.02 £	201.09 ± 5.02 £	200.09 ± 5.02 £	198.09 ± 4.90 £
Body weight	Day 28	210.40 ± 4.52	143.00 ± 6.14 φ	210.07 ± 6.04 £	208.07 ± 5.04 £	206.07 ± 6.04 £	205.05 ± 6.04 £
TC (mg/dL)	Day 0	78.78 ± 2.44	183.38 ± 4.42 φ	89.38 ± 3.00 £	88.36 ± 2.25 £	85.32 ± 2.98 £	84.32 ± 2.51 £
Lipid profile TG (mg/dL)	Day 7	111.75 ± 2.36	164.10 ± 2.43 φ	107.05 ± 4.40 £	106.95 ± 4.40 £	106.15 ± 4.48 £	105.50 ± 4.30 £
HDL (mg/dL)	Day 14	30.14 ± 0.98	22.68 ± 1.11 φ	27.18 ± 1.21 £	27.98 ± 1.31 £	26.10 ± 1.65 £	25.10 ± 1.54 £
LDL (mg/dL)	Day 21	30.40 ± 1.51	103.42 ± 2.90 φ	36.51 ± 2.51 £	36.95 ± 2.57 £	36.54 ± 2.41 £	36.05 ± 2.39 £
HDL (mg/dL)	Day 28	25.12 ± 0.48	20.22 ± 1.14 φ	25.14 ± 1.11 £	25.12 ± 1.02 £	25.00 ± 1.05 £	24.14 ± 1.02 £

The values indicate the mean SD. Compared with normal control and treatment, the difference between the mean and the treatment values is insignificant

The values indicate the mean SD. Compared to normal control and treatment, the difference between the values of these drugs and those of the placebo is not significant.

Table.4 Effect of Moringa oleifera (SEDDS) on Liver Function Tests

Sr.NO	NC	DC	Standard	F1	F2	F3
Liver function tests AST (U/L)	51.72 ± 1.01	98.24 ± 2.78 φ	59.71 ± 2.25 £	58.60 ± 2.02 £	57.71 ± 2.25 £	56.81 ± 2.25 £
ALT (U/L)	68.14 ± 2.06	111.06 ± 4.95 φ	70.75 ± 3.87 £	70.95 ± 2.87 £	70.75 ± 3.35 £	70.20 ± 3.45 £
ALP (U/L)	117.63 ± 3.44	213.30 ± 5.63 φ	142.59 ± 3.50 £	142.50 ± 3.00 £	142.95 ± 3.10 £	143.02 ± 3.20 £

Serum urea (mg/dL)	38.70 ± 1.36	68.54 ± 2.43 φ	41.20 ± 1.16 £	41.85 ± 1.10 £	41.98 ± 1.15 £	41.25 ± 1.20 £
KFT Serum creatinine (mg/dL)	0.91 ± 0.06	1.34 ± 0.06 φ	0.92 ± 0.07 £	0.93 ± 0.06 £	0.93 ± 0.08 £	0.94 ± 0.03 £
Uric acid (mg/dL)	8.41 ± 0.23	19.05 ± 0.96 φ	8.56 ± 0.89 £	8.50 ± 0.44 £	8.68 ± 0.90 £	8.98 ± 0.62 £
SOD (U/mg protein)	9.10 ± 0.09	5.82 ± 0.11 φ	8.83 ± 0.06 £	8.60 ± 0.05 £	8.65 ± 0.07 £	8.92 ± 0.05 £
Antioxidant status CAT (U/mg protein)	66.37 ± 2.33	47.07 ± 2.61 φ	60.80 ± 1.72 £	60.95 ± 1.82 £	61.20 ± 1.25 £	61.90 ± 1.74 £
GSH (U/mg protein)	12.73 ± 0.87	6.27 ± 0.80 φ	9.27 ± 0.93 €	9.10 ± 0.83 €	9.72 ± 0.54 €	9.93 ± 0.79 €
Antioxidant status TNF-α	52.28 ± 3.47	179.08 ± 7.54 φ	82.95 ± 3.17 £	83.20 ± 2.87 £	83.55 ± 2.37 £	83.95 ± 2.47 £
IL-6	40.42 ± 3.29	108.75 ± 5.14 φ	68.19 ± 2.91 £	68.39 ± 2.95 £	68.69 ± 1.56 £	69.19 ± 2.71 £

Effect of Moringa oleifera on Kidney Function Test in Diabetic Rats

Table 2 summarizes the results of the various kidney function tests, biochemical tests, and liver function tests that were performed. The former group had impaired kidney function, while the latter showed improvement. After the treatment with Moringa Oleifera, the levels of uric acid, urea, and creatinine were returned to normal. Moringa oleifera results were better, while GLB had similar results.In terms of uric acid and urea, both GLB and Moringa olifera exhibited similar results, while in the case of creatinine, the former performed better than the latter. Both treatments could result in a significant improvement in kidney function.

Effect of Moringa oleifera on Antioxidant Status

Table 1 shows the results of the GSH, CAT, and SOD expression in the different groups. The DC group exhibited a significant decrease in the expression of these substances compared to the NC group. Upon treatment with GLB and Moringa oleifera SEDDS,the expression of these substances returned to a normal level.Similar results were observed for GSH, SOD, and GLB, suggesting that an increase in antioxidant enzymes can help alleviate DM. On the other hand, in CAT, the results were slightly better.

Histo-pathological studies

Histological and biochemical studies of diabetic rats revealed that the use of Moringa oleifera SEDDS significantly improved their histological and molecular characteristics. It also exhibited a beneficial effect on the regeneration of pancreatic beta-cells. In addition, it has the potential to be utilized as an antioxidant and prophylactic supplement for treating diabetes.

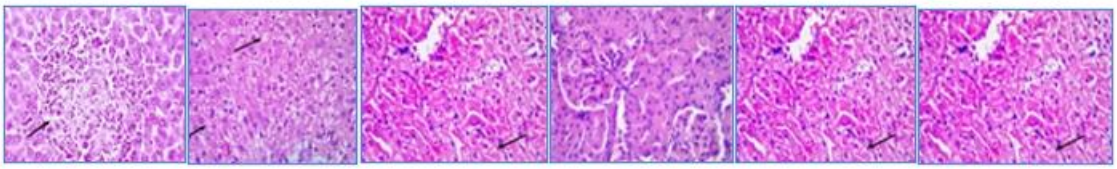

Fig. 5a. Normal Control b. Disease control c. Standard (GLB)d. F1(MO SEDDS) e. F2(MO SEDDS) f. F3(MO SEDDS)

The photomicrograph shows the normal histological picture of hepatic sections in normal control and Moringa oleifera SEDDS non-diabetic rats. In contrast, in diabetic rats, the focal necrosis and acute cellular swelling are caused by mononuclear cells. In Moringa oleifera SMEEDS therapeutic rats, the fatty change is caused by micro-vesiculation.

DISCUSSION

The present study demonstrated that formulation of Moringa oleifera leaf extract as a self-emulsifying drug delivery system (SEDDS) significantly enhanced its pharmacological efficacy against streptozotocin-induced diabetes in albino rats. The improved antihyperglycemic and antioxidant activity can be attributed to the increased solubility, rapid dispersion, and enhanced intestinal absorption of bioactive phytoconstituents such as quercetin and kaempferol through the nanoemulsified system. The optimized SEDDS showed superior stability, smaller droplet size, and uniform distribution, which facilitated better bioavailability and consistent therapeutic response. Moreover, biochemical and histopathological findings indicated marked restoration of pancreatic and hepatic architecture, supporting the protective effect of the formulation against oxidative stress and metabolic disturbances associated with diabetes.

CONCLUSION

In conclusion, Moringa oleifera-based SEDDS offers a promising phytopharmaceutical approach for effective diabetes management by improving solubility, absorption, and biological activity of plant-derived compounds. The study validates the potential of lipid-based delivery systems in enhancing the therapeutic performance of herbal extracts. Further pharmacokinetic and clinical investigations are warranted to establish its long-term safety and efficacy for translational application.

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