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FORMULATION, CHARACTERISATION AND ANTI DIABETIC EVALUATION OF *TALINUM PORTULACIFOLIUM* (FORSSK.) LOADED SOLID LIPID NANOPARTICLES IN STREPTOZOTOCIN & HIGH FAT DIET INDUCED DIABETIC RATS

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ABSTRACT

Diabetes mellitus is a complex metabolic disease characterized by severe hyperglycaemia and huge metabolic disturbances. In this present study we have loaded ethanolic extract of *Talinum portulacifolium* (Forssk.) (EETP) in to suitable lipids to prepare solid lipid nanoparticles using ultrasonication homogenization method to improve the solubility and in turn the bioavailability of extract. We have evaluated both extract and SLN of *Talinum* (T-SLN) for anti diabetic activity in streptozotocin and high fat diet induced diabetic rats. The parameters like Blood glucose level, serum insulin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), lipid peroxidase, catalase, glutathione were evaluated in normal and diabetic rats. Our results showed that SLN of *Talinum* (T-SLN) treatment reduced all the elevated parameters tested in the rats at doses of 250 mg/kg. Histopathological studies of pancreas of these animals showed comparable regeneration on treatment with T- SLN. Glibenclamide was used as a standard drug at a dose of 0.5mg/kg.

Keywords: Antidiabetic activity, Histopathology, Streptozotocin, High fat diet, *Talinum portulacifolium,* Solid lipid nanoparticles, Glibenclamide.

INTRODUCTION:

Solid lipid nanoparticles are the type of pharmaceutical formulation. Particulate systems such as nanoparticles are used as a physical approach for altering and improving pharmacokinetic and pharmacodynamic properties of different types of drug molecules**.** For increasing the bioavailability and consisting of well tolerated excipients of drug carrier formulations, Solid Lipid Nanoparticles (SLN) are alternative drug carrier systems **(Peters K *et al*., 1996).** In contrast to liposomes and emulsions, the particle matrix of SLN is made up of solid lipids.

Diabetes mellitus is a group of metabolic disorders, it is very complicated, chronic disorder characterized by either insufficient production of insulin by β-cells of pancreatic cells or due to cellular resistance to insulin. It is one of the most common metabolic syndromes. Recent approach states that traditional plants show better effect than currently using drugs **(Rates 2001)**. The leaves of *Talinum portulacifolium* (Forssk.) are eaten as a cooked vegetable or raw as a salad, alone with young stem parts. The genus *Talinum* consists of 500 species mainly in the regions of South Africa & America **(Heywood 1978).** It is perennial, shrubby plant distributed from Rajasthan in our country. It is cultivated in Africa as Spinach, it is also said to have aphrodisiac activity **(Anonymous 1974).** The leaf powder of this plant is mixed with boiled milk & taken twice a day for treating Diabetes **(Reddi et al., 2004).** For a long time the tribal people of the Rayalaseema region in Andhra Pradesh, India have used the leaves of the plant *Talinum portulacifolium* (Forssk.) to keep away from Diabetes and widely used as a vegetable **(Nagaraju & Rao 1989).** Our previous studies shown significant Antidiabetic activity in Alloxan – Induced diabetic rats **(Mandal et al., 2007)** and Streptozotocin induced diabetes **(Nageswar Rao et al., 2011).**

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MATERIALS & METHODS

Plant Material:

The whole plant *Talinum portulacifolium* (Forssk.) (Portufoliaceae) was collected from Tirumala hills, Tirupathi, India in the month of December 2013 and was identified and authenticated (PARC/2014/2299) by Dr. P. Jayaraman, Director, National Institute of Herbal Medicine, Plant Anatomy Research Centre, Chennai.

Chemicals:

Streptozotocin was acquired from BROS chemicals, Tirupathi, Andhra Pradesh, India Glibenclamide, Tween-80, Phosphate buffer, Ethanol were acquired from chemical stores of Sree Vidyanikethan College of Pharmacy, Tirupathi, Andhra Pradesh, India.

Preparation of extract:

The collected plant was washed and surface sterilized to remove unwanted matter from the plant. Then it was shade dried under room temperature. Ground in dry grinder and passed through sieve to get fine powder. About 50 gm of the powder was packed in to soxhlet apparatus and defatted with petroleum ether (60-80^{0}C). Marc left was further extracted with ethanol. Extract was air dried until it comes to semi-solid to solid mass. Then it was stored in refrigerator below 10^{0}C. The yield of ethanolic extract obtained was found to be 15.00%w/w. Then the solid lipid nanoparticles were formulated using the extract.

Preliminary Phytochemical Screening:

The Preliminary phytochemical studies were conducted for the ethanolic extract of

Talinum portulacifolium as per the standard procedures and the extract was identified with presence of various phytoconstituents like carbohydrates, alkaloids, glycosides, flavonoids, phenolic compounds, steroids, triterpenoids and tannins.

Preparation of Formulation:

Lipids (organic phase) were melted by using hot plate at 70^{0}C. Then the plant extract (aqueous phase) was added. Simultaneously surfactant (Tween-80) was mixed with phosphate buffer until it gets miscible, pH was maintained at 7.4. Then aqueous phase was added to organic phase slowly by injection method, with high shear homogenization at 20,000 rpm. This process was repeated for 4-5 times followed by ultrasonication for 10-15 min. Finally SLN loaded with *Talinum portulacifolium* were formed, which was further evaluated.

Characterization of solid lipid nanoparticles

Determination of P^H

The P^H was determined by using digital P^H meter. 50ml of herbal formulation was taken in beaker. Then the bulb of the P^H meter was dipped into the formulation and the P^H was measured precisely **(Mason TG *et al*., 2006)**

Measurement of particle size, polydispersity index and zeta potential

Particle size distribution of *Talinum portulacifolium* loaded Solid lipid nanoparticles T-SLN and ethanolic extract were determined by laser scanning technique by using Nanoparticle SZ-100 (Horiba Company, Japan) instrument after appropriate dilution with double distilled water. The mean particle size, polydispersity index and zeta potential were calculated for T-SLN and herbal extract maintained at 25^{0}C and polydispersity index used to measure the size distribution population of nanoparticles **(Yang SC *et al*., 1999)** and the results were shown in the figures 2 & 3.

Scanning Electron Microscopy

The SEM analysis was carried out using a scanning electron microscope (LEO, 435 VP, U.K). Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 5 KV and resolution of 4000 **(Mukherjee S *et al.*, 2007)**

Fourier Transform Infrared (FTIR) spectroscopic analysis

The FTIR analysis of EETP and EETP loaded SLN's (T-SLN) were carried out by using Agilent Resolution Pro instrument (US). The FTIR spectra of EETP and T-SLN were recorded using FTIR spectrophotometer in the range of 4000-650 cm^{-1}

Animals

Albino wistar rats of both the sexes (150-180g) obtained from animal house of Sree Vidyanikethan College of Pharmacy were used for this experiment. The animals were housed under standard environmental conditions (22±5ºC with12 h of light/dark cycle) and fed with commercial rat feed (Lipton India Ltd., Mumbai, India) and water, *ad libitum*. All animal experimental protocols were approved by Institutional Animal Ethical Committee (SVCP/ IAEC/ I-020/2013-2014).

High fat diet:

The Normal rat diet contains 54% car-bohydrate, 13.2 kJ/g calories, 4% lipid. The high-fat diet was consisting of 40% standard diet, 5.1% carbohydrate, 20% eatable lard, 34% egg (w/w) and 0.9%NaCl, in which the calorie of diet was 22.1 kJ/g, and fat 60.17%, saccharides 25%, **(Tian *et al.*, 2006).**

Acute toxicity studies:

Acute oral toxicity studies were performed as per OECD - 423 guidelines, albino wistar rats of either sex selected by random sampling technique were used for acute toxicity study. At first the animals were kept fasting for overnight providing only water, later the extract prepared was administered orally at the dose level of 5 mg/kg body weight by gastric intubation & observed in 2 out of 3 animals, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for further higher doses such as 50, 300 & 2000 mg/kg body weight.

Experimental design:

In this experiment 40 rats were used. The rats were rendered diabetic by the oral feeding of high fat diet for 2 weeks initially and injection of STZ (45mg/kg) through intraperitoneal (i.p) route. The animals with blood glucose levels above 350 mg/dl were selected for the study. Further these rats were divided into four groups (Group II, II, IV and V) six in each group after the induction of diabetes. Group I rats were fed with normal pellet diet.

Group I: Normal control rats (saline)

Group II: Diabetic control rats (High fat diet for 2 weeks & STZ 45 mg/kg. ip)

Group III: Inducing agent (STZ 45 mg/kg. ip) + Standard drug (glibenclamide 5mg/kg P.O)

Group IV: Inducing agent (STZ 45 mg/kg. ip) + Herbal ethanolic extract (250mg/kg P.O)
Group V: Inducing agent (STZ 45 mg/kg. ip) + T-SLN (P.O)

Biochemical Estimations

After 28 days of the study, blood samples were collected from the retro orbital plexus of experimental animals. Blood glucose and serum lipids such as Total cholesterol (TC), Triglycerides (TG), Low density lipoproteins (LDL) and High density lipoproteins (HDL), SGOT, SGPT, Glutathione, Catalase, Lipid Peroxidase were estimated.

Histopathological studies

Pancreas from rats were fixed in 10% neutral formalin solution, dehydrated in alcohol and embedded in paraffin and counter-stained with Hematoxylin & Eosin for light microscopic analyses.

Statistical analysis

The results were presented as Mean ± S.E.M (n=6 in each group). Analyses were performed using One-way ANOVA followed by Dunnett's multiple for the difference between the control and treatment groups.

RESULTS

Preliminary phytochemical screening:

S. No.	Chemical Constituents	Ethanolic Extract
1	Carbohydrates	_
2	Proteins & Amino acids	_
3	Glycosides	+
4	Flavanoids	+
5	Alkaloids	_
6	Saponins	+
7	Tannins	+
8	Steroids	+
9	Phenols	+

EETP indicates Ethanolic extract of *Talinum portulacifolium*
"+" indicates Present
"-" indicates absent

Characterization:

PH:

PH and viscosities of the formulation are in same range without any much deviation, PH of the herbal formulations are found to be nearly neutral i.e. 7.

Scanning electron microscopy (SEM)

The SEM photograph (Figure 1) of optimized formulation reveals that T-SLN was spherical and moderately uniform in size.

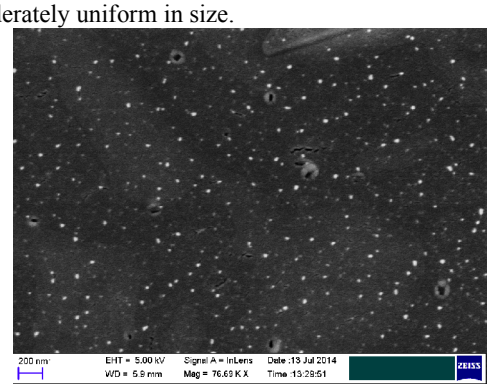

Fig 1: SEM analysis of Solid lipid nanoparticles

Particle size determination

The measurement of zeta potential allows for prediction about the storage stability of colloidal particles, as the particle aggregation will be less to the charged particles. For the prepared SLNs the Zeta Potential (mV), particle size and polydispersity index are tabulated below.

Zeta potential, particle size and polydispersity index of SLN Formulation

S. No	Formulation	Size average (nm)	Polydispersity index (PI)	Zeta potential
1.	SLN	260	0.543	-27.7Mv

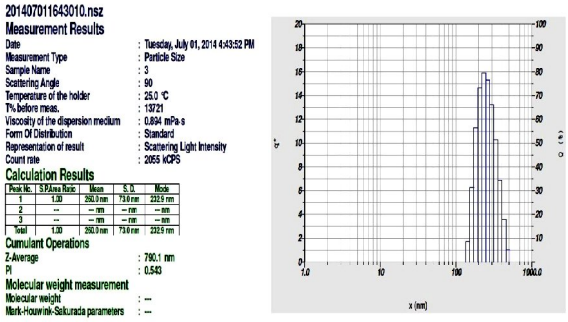

Fig 2: shows Zeta size analysis

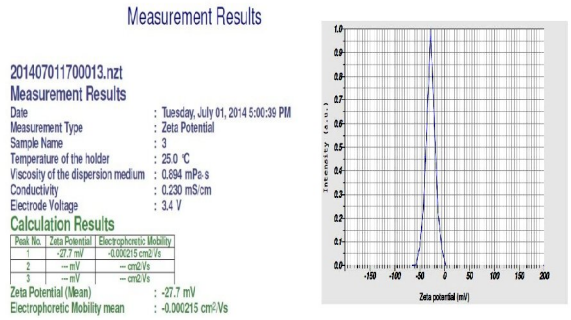

Fig 3: shows Zeta potential analysis

FT-IR Analysis

The FT-IR spectroscopy is used to investigate the interactions between lipid, extract and other excipients. From the FT-IR spectra of EETP, optimised formulation of SLN it is confirmed that there is decrease in intensity of peak at 3317 cm^{-1} corresponding to OH group and 2972 corresponding to CH stretching compared to FT-IR spectra of EETP was observed. Presence of strong peak at 1619 cm^{-1} and dual peaks at 1397, 1334 cm^{-1} indicates COOH group present in EETP was involved in hydrogen bonding, Presence of Strong peak at 1043 indicates C=O. These predictions ensures that the interactions between lipid molecules of SLN with the EETP.

The FTIR spectra of EETP (Fig 4) and T-SLN (Fig 5) were recorded using FTIR spectrophotometer in the range of 4000-650 cm^{-1} and the interpretation results were shown in the table.

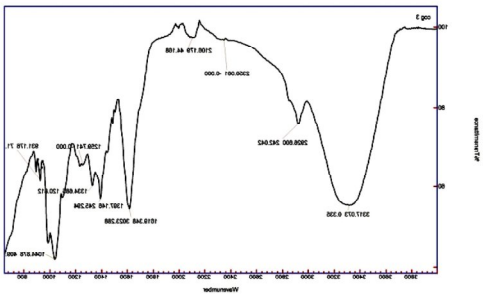

Fig 4: FTIR spectra of EETP leaves

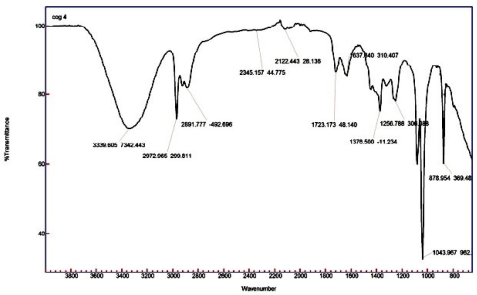

Fig 5: FTIR spectra of SLN formulation

Acute toxicity studies

The EETP and T-SLN were found to be safe since no animal died even at the dose of 2000 mg/kg when administered orally and the animals did not show any gross behavioral changes.

Blood glucose estimation:

Determination of blood glucose Fasting blood glucose was estimated by commercially available glucose strips (Accu-Chek) using One Touch Glucometer (Johnson – Johnson, India). Estimation of blood glucose level on 0^{th} day, 7^{th} day, 14^{th} day, 28^{th} day.

ESTIMATION OF BIOCHEMICAL PARAMETERS:

Biochemical Parameters like cholesterol, triglycerides high density lipids, low density lipids were estimated and show significant decrease in elevated levels of those parameters.

IN VIVO ANTIOXIDANT STUDIES:

Anti oxidant enzymes like glutathione, lipid peroxidase, SGOT, SGPT, catalase were estimated and shown significant decrease in the elevated levels.

Table 1: Blood glucose Estimation

GROUPS	0^{TH} DAY	7^{TH} DAY	14^{TH} DAY	28^{TH} DAY
CONTROL	101.2±0.87*	102±0.91*	102.2±0.87*	99.33±0.76*
NEGATIVE CONTROL	232±2.9*	232.5±2.9*	237.8±1.68*	239.7±0.98*
STANDARD	232±3.1*	159.7±1.9*	118.8±1.40*	113.2±0.90*
ETHANOLIC EXTRACT	234±3.1*	178±1.24*	160.2±1.16*	147.5±0.76*
FORMULATION	237.5±3.1*	164±1.72*	131.0±2.62*	128.2±o.70*

Data are expressed as Mean ± S.E.M (n=6), One-way ANOVA Dunnet's multiple comparison tests; *p≤0.001

Table 2: Biochemical Parameters

GROUPS	CHOLESTEROL	TRIGLYCERIDE	HDL	LDL
CONTROL	68.46±1.78	67.5±1.05	33±0.73	27.5±0.42
N.CONTROL	135.8±1.22*[a]	165.8±0.7*[a]	18.5±0.61*[a]	80.17±0.6*[a]
STANDARD	75±1.29**[b]	81.5±1.47**[b]	29.67±0.61**[b]	31.5±0.76**[b]
EETP(250mg/kg)	79.83±2.13*[b]	93.17±1.68*[b]	23±0.73*[b]	42.33±1.0*[b] 5
T-SLN(250mg/kg)	75.5±1.2**[c]	85.67 ±1.76**[c]	28.5±0.56**[c]	35.5±1.23**[c]

Values are expressed as Mean ± SD; n=6, P<0.001 STZ (45mg/kg) was injected to control and all other drug treated groups; [a] STZ induced diabetic group Vs normal group, *p <0.001; [b] extract treated group vs STZ induced diabetic group, *P< 0.01; [c] T-SLN treated group vs STZ induced diabetic group, **P <0.001

Table 3: Estimation of SGOT & SGPT

S. No	Parameters	Control	N. Control	Standard	EETP 250mg/kg	T-SLN 250mg/kg
1	SGOT	102.00±7.62	124.33±3.56*[a]	103.50±3.02**[b]	106.33±7.15*[b]	106.33±7.15*[c]
2	SGPT	60.92±6.47	93.00±4.05*[a]	55.67±3.14**[b]	60.50±4.46*[b]	52.59±4.24*[c]

Values are expressed as Mean ±SD; n=6, P<0.01; Values are expressed as Mean ± SD; n=6, P<0.001 STZ (45mg/kg) was injected to control and all other drug treated groups; [a] STZ induced diabetic group Vs normal group, *p <0.001; [b] extract treated group vs STZ induced diabetic group, *P< 0.01; [c] T-SLN treated group vs STZ induced diabetic group, **P <0.001

Table 4: *In vivo* antioxidant studies

GROUPS	LIPID PEROXIDASE (µM/mg tissue)	GLUTATHIONE (µM/mg tissue)	CATALASE (µM/mg tissue)
Control	0.81±0.08	1.6±0.01	2.2±0.01
N. Control	1.9±0.13*[a]	0.73±0.01*[a]	0.82±0.09*[a]
Standard	0.93±0.07**[b]	1.4±0.01**[b]	2.0±0.03**[b]
EETP(250mg/kg)	1.3±0.06*[b]	1.2±0.02*[b]	1.4±0.02*[b]
T-SLN(250mg/kg)	0.99±0.02**[c]	1.3±0.02**[c]	1.9±0.02**[c]

Values are expressed as Mean ±SD; n=6, P<0.01; Values are expressed as Mean ± SD; n=6, P<0.001 STZ (45mg/kg) was treated group vs STZ induced diabetic group, *P< 0.01; [c] T-SLN treated group vs STZ induced diabetic group, **P <0.001injected to control and all other drug treated groups; [a] STZ induced diabetic group Vs normal group, *p <0.001; [b] extract

Histopathology Studies:

After 28 days of total study, rat from each group were anesthetized. The Pancreas was removed from the each rat and was excised quickly and fixed in 10% buffered- formaldehyde at room temperature. After dehydration using graded ethanol, pieces of tissues were embedded in paraffin, and 5 micrometer thick sections were cut by a rotator microtome and mounted on glass slides. Sections were then de-paraffinized with xylene, and then counterstained with hematoxylin and eosin. The Histopathology results were shown in following figure.

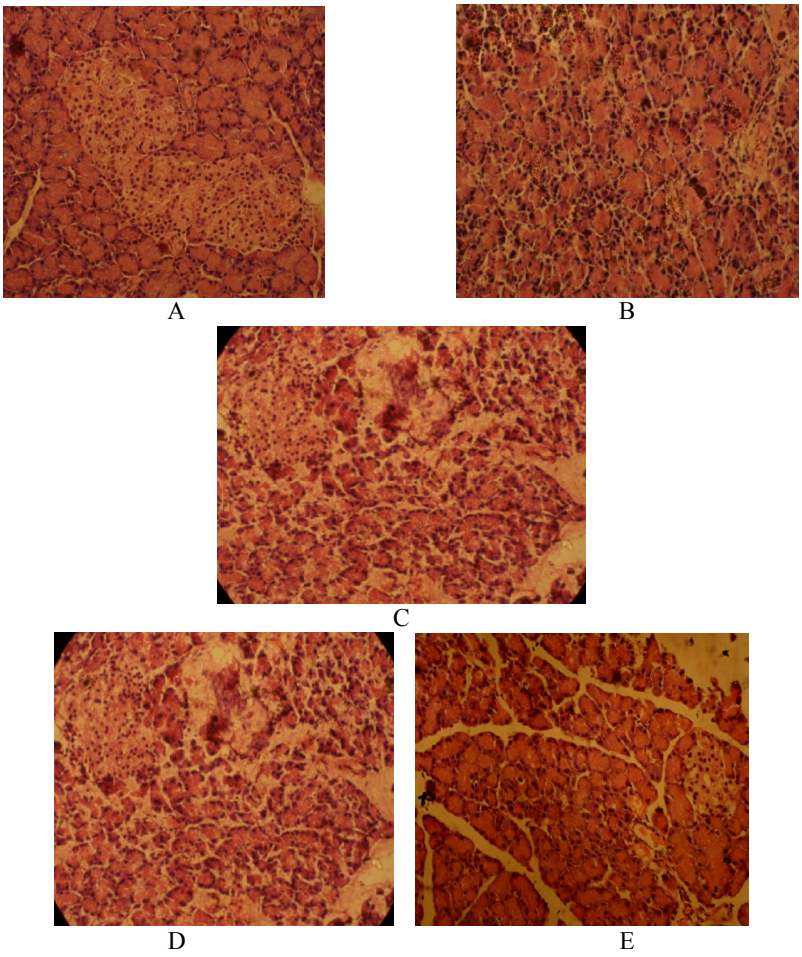

Figure 1: Histopathological study of Pancreatic cells; (A) normal cells; (B) Negative control; (C) Pancreas treated with Standard drug (D) Pancreas treated with 250 mg/kg of Ethanolic Extract (E) Pancreas treated with 250 mg/kg of T-SLN

DISCUSSION & CONCLUSION:

Talinum portulacifolium (Forssk.) is a well known traditional medicinal plant for its pharmacological function and diverse biological activities including reducing blood glucose levels, serum lipids and anti-oxidant enzymes. It has been used to treat diabetes mellitus **(Mandal SC *et al*., 2007).** Increased levels of blood glucose in turn increase lipids, which results in cardiovascular disorders.

Talinum portulacifolium (Forssk.) was extracted with ethanol and T-SLN was prepared by using ultrasonic homogenization method. The T- SLNs were characterized by Scanning Electronic Microscopic analysis. Iit was observed that T-SLN dispersion showed spherical shaped particles and mean particle size of T-SLN was found to be 260 nm and the pH was 7. FTIR studies was performed for extract and T- SLNs and showed no interaction between extract and excipients uesd in the formulation.

Streptozotocin is used for the induction of experimental diabetes mellitus in animals **(Nageswar Rao *et al* 2011)**. It has a destructive effect of the beta cells of the pancreas **(Szkudelski T, 2001)** Streptozotocin causes a massive reduction in insulin release by the destruction of beta-cells of the islets of langerhans thereby inducing hyperglycemia **(Lenzen S *et al*., 1988).** Insulin deficiency leads to various metabolic alterations in the animals viz increased blood glucose and increased lipid profile. The results of the present study found that the ethanolic extract of *Talinum portulacifolium* reduced the glucose level in animals which were made diabetic with STZ and High fat diet. Streptozotocin has been shown to induce free radical production and cause tissue injury. The pancreas is especially susceptible to the action of STZ induced free radical Damage. The present investigation demonstrated ethanolic extract of *Talinum portulacifolium has* the significant anti-diabetic Activity, and also reduced the levels of serum lipids. The antihyperglycemic effect of the ethanolic extract may be due to the enhanced secretion of insulin from the beta cells of pancreas or may be due to increased tissue uptake of glucose by enhancement of insulin sensitivity. Diabetic rats showed elevated plasma cholesterol, triglycerides and LDL which are the major risk factors of cardiovascular diseases. Ethanolic Extract and T-SLN in the dose of 250 mg/kg reduced the lipid profile along with the reduction in the blood glucose levels. The literature report reveals that flavonoids and tannins present in the plant extract were known to possess antihyperglycemic and hypolipidemic activity **(Higdon, Jet al., 2009)**. The present investigation also observed antihyperglycemic and hypolipidemic potential of test extracts which may be due to presence of similar phytoconstituents which were evident by preliminary phytochemical screening. Since many antihyperglycemic drugs do not correct dyslipidemia, the observed hypolipidemic effects of the plant extract and formulation in diabetic rats marks importance in management of diabetes. Since there is a strong well-established link between diabetes mellitus, dyslipidemia, obesity, hypertension and ischemic heart disease, effect of the plant extract and formulation on weight loss/gain needs to be explored on scientific base.

It is concluded that the ethanolic extract of *Talinum portulacifolium* (Forssk.) (EETP and Nano formulation (T-SLN) at the dose of 250 mg/kg body weight produced significant antidiabetic activity in Streptozotocin and High fat diet induced Diabetic rats. It is also found to be highly effective in managing the complications associated with diabetes mellitus, such as hyperlipidaemia, and prevents the defects in lipid metabolism.

Therefore, *Talinum portulacifolium* (Forssk.) shows therapeutic promise as a protective agent against the development and progression of possible cardiovascular complications in diabetes mellitus**.** In addition, the Anti-Diabetic property may be attributed to the active constituents in the plant namely, flavonoids and Tannins.

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