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Streptozotocin-induced Antidiabetic Activity of *Vitex negundo*, *Vitex trifolia* and *Vitex parviflora* Combined Phytosomal Formulation

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Multifactorial metabolic diseases, for instance diabetes develop several complications like hyperlipidemia, hepatic toxicity, immunodeficiency etc., Hence, instead of mono-drug therapy the management of the disease requires the combination of herbs. Marketed herbal drugs comprise of irrational combinations, which makes their quality control more difficult. Phytoconstituents, despite having excellent bioactivity *in vitro* demonstrate less or no *in vivo* actions due to their poor lipid solubility, resulting in high therapeutic dose regimen; phospholipids encapsulation can overcome this problem. Hence, present study was designed to develop a phospholipids encapsulated polyherbal antidiabetic formulation. The prepared *Vitex negundo, Vitex trifolia* and *Vitex parviflora* leaves extract and phytosomal formulation were studied for the acute oral toxicity and anti-diabetic activity against streptozotocin-induced rat's model. The antidiabetic activity was compared with control group, the standard drug Glibenclamide (500 mcg/kg /po), leaves extracts and its phytosome formulation (100 and 200 mg/kg/po). Acute toxicity studies show no mortality and morbidity up to the dose 2000mg/kg of body weight. In this study, body weight, serum glucose levels, total cholesterol, triglyceride, HDL, LDL, and total protein were measured. The results showed that there was a significant decrease ($P<0.05$) in the serum glucose levels, cholesterol, total protein, LDL and triglyceride levels in diabetic rats when compared to the normal (control) rats and increase the level of HDL and body wt. Further the research proves that phytosome formulation is superior in controlling blood sugar than *Vitex negundo, Vitex trifolia* and *Vitex parviflora* leaves extract.

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1. INTRODUCTION

Diabetes mellitus is a systemic metabolic disorder characterized by increase in blood glucose due to insufficient secretion of insulin and lack of insulin action. It also involves hyperaminoacidemia and hyperlipedemia. Neuropathy, nephropathy, cardiovascular and cerebrovascular diseases are some of the complications frequently associated with diabetes [1]. Managing diabetes without any side effects is a challenge, as presently available drugs for diabetes have undesired harmful effects. Thus, the search for new anti diabetic agent continues [2]. The emerging technology of drug delivery and drug targeting is being applied to phytopharmaceuticals in recent time. The major factors for drug molecules to pass through the biological membranes to be absorbed systematically are lipid solubility and their size. In spite of having excellent bio-activity *in vitro*, many of the plant extracts and phytomolecules results in poor absorption and bioavailability due to their poor lipid solubility and improper molecular size [3]. The bioavailability of lipophilic drugs is low when administered orally due to slow or incomplete dissolution in the lumen of the gastrointestinal tract. Phospholipids play a major role in development of novel phytopharmaceuticals because of their biocompatible nature with the phytochemicals. Several studies have suggested the beneficial role of phospholipids in enhancing the therapeutic efficacy of phytochemicals having poor oral absorption [4]. Therefore, a novel approach is essential to increase the bioavailability of such compounds for better clinical utility [5]. For better bioavailability and faster actions of herbal extracts/constituents, novel drug delivery systems such as phytosomes or herbosomes are used. Phytosomes are novel phytoformulations that contain active phytoconstituents encapsulated within the lipid layer. Phytosomes shows better absorption since the water soluble constituent is covered by a lipophilic outer layer and hence show better bioavailability than the conventional herbal extracts [6]. The phytosomes of *Ginkgo biloba* [7], grape seed [8], green tea [8], milk thistle [9] hawthorn [10] and ginseng [10] proved this by improving the bioavailability. This technology has also been applied for flavanoids and polyphenolic compounds [11,12]. To the best of our knowledge no scientific data on the preparation of *Vitex negundo, Vitex trifolia*, *Vitex parviflora,* phospholipid complex (phytosome) is available in literature. Hence, the present work aims to prepare and evaluate phytosome complex of *Vitex negundo, Vitex trifolia*, *Vitex parviflora,* standardized extract for antidiabetic activity in diabetic rats.

2. MATERIALS AND METHODS

2.1 Plant material

Leaves of *Vitex negundo, Vitex trifolia* and *Vitex parviflora* were collected from ruler area of Bhopal, Bhimbetka Bhojpur and Vindhya Herbals Bhopal respectively in the month of February, 2019. Plant material (leaves part) selected for the study were washed thoroughly under running tap water and then were rinsed in distilled water; they were allowed to dry for some time at room temperature. Then the plant material was shade dried without any contamination for about 3 to 4 weeks. Dried plant material was grinded using electronic grinder. Powdered plant material was observed for their color, odor, taste and texture. Dried plant material was packed in air tight container and stored for phytochemical and biological studies.

2.2 Chemical Reagents

All the chemicals used in this study were obtained from Hi Media Laboratories Pvt. Ltd. (Mumbai, India), Sigma Aldrich Chemical Co. (Milwaukee, WI, USA), SD Fine-Chem. Ltd. (Mumbai, India) and SRL Pvt. Ltd. (Mumbai, India).All the chemicals used in this study were of analytical grade. Streptozotocin (Sigma-Aldrich), biochemical estimation kit (Transasia Bio Medical Limited, Mumbai, India) and glibenclamide tablets (Daonil; Aventis Pharma. Ltd., India) were procured from the medical store.

2.3 Defatting of Plant material

The shade dried leaves of *Vitex trifolia* (100gm), *Vitex negundo* (75 gm) and *Vitex parviflora* (124gm) were extraction with petroleum ether using maceration method. The extraction was continued till the defatting of the material had taken place.

2.4 Extraction with Single Solvent (Hydroalcoholic) by Maceration Method

The air-dried and powdered defatted marc of leaves of *Vitex negundo, Vitex trifolia* and *Vitex parviflora* were subjected to extraction with ethanol: water in ratio of 80:20 v/v by maceration method. The resultant content was filtered with whatman filter paper no.1 and kept for evaporation of solvent to get the dry concentrated extract. The dried crude concentrated extract was weighed to calculate the extractive yield then transferred to glass vials (6 ×2 cm) and stored in a refrigerator (4°C), till used for analysis [13].

2.5 Formulation of Phytosomes

Phytosomes of combined extracts of *Vitex negundo, Vitex trifolia* and *Vitex parviflora* prepared by reflux method. The specific amount of leaves of *Vitex negundo, Vitex trifolia* and *Vitex parviflora* extract and soya lecithin was placed in a 100ml round-bottom flask and 50ml of methanol was added as reaction medium. The mixture was refluxed and the reaction temperature of the complex was controlled to 50°C for 3 h. The resultant clear mixture was evaporated and 20 ml of n-hexane was added to it with stirring. The precipitated was filtered and dried under vacuum to remove the traces amount of solvents. The dried residues were gathered and placed in desiccators overnight and stored at room temperature in an amber colored glass bottle [14].

2.6 Screening of Anti-diabetic Activity

2.6.1 Animals

Wistar rats (150-200 gm) were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2°C, 55-65%). Rats received standard rodent chow and water *ad libitum*. Rats were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of rats was used for each set of experiments.

2.6.2 Toxicity study

Healthy adult male albino rats were fasted overnight prior to the experiment. Different doses (50-2000 mg/kg, P.O) of the hydroalcoholic extract leaves of *Vitex trifolia, Vitex negundo, Vitex parviflora* and phytosomal formulation were administered to each group of rats (Each group carries 6 rats) and they were observed continuously for 1 hour and then at half-hourly intervals for 4 hour, for any gross behavioural changes and further up to 72 hour, followed 14 days for any mortality as per the OECD (Organization for Economic Co-operation and Development) Guideline 425 [15]. The hydroalcoholic leaves extract of *Vitex trifolia, Vitex negundo, Vitex parviflora* and phytosomal formulation was found to be non-toxic up to the maximum dose of 2000 mg/kg body weight. Dose selected for anti-diabetic evaluation was 100 and 200mg/kg respectively.

2.6.3 Induction of experimental diabetes in rats

Rats were divided into different groups, each group consisting of six animals. After overnight fasting (deprived of food for 16 hours had been allowed free access to water) diabetes was induced in group II-XI by intraperitoneal injection of STZ dissolved in O.1M sodium citrate buffer at pH 4.5, at a dose of 55mg/kg body weight. The control rats received the same amount of 0.1 M sodium citrate buffer. The animals were allowed to drink 5% glucose solution overnight to overcome the drug-induced hypoglycemia. Diabetes status was confirmed by estimating blood glucose levels after 72 hours of STZ injection. Animals showing fasting blood glucose levels above 250 mg/dl were selected for study.

Body weight of rats was taken on pre and post treatment i.e. initial and final day of post treatment by electronic balance. Fasting blood glucose level of rats were taken pre and post treatment i.e. 0, 8^{th} and 21^{th} day of post treatment. At the end of experimental period, all the rats were sacrificed by cervical decapitation. Blood samples were collected, allowed to clot. Serum was separated by centrifuging at 2500 rpm for 15 min and analyzed for various biochemical parameters [16, 17].

2.7 Statistical Analysis

Variables of interest were entered and all data analyzed using Graph Pad Instant 3.06 software version 14 for windows XP (Microsoft Corporation). All statistical analysis is expressed as mean ± standard error of the mean (SEM).

List 1. Grouping of animals

Group I	**Normal**
Group II	Diabetic control received only STZ (negative control)
Group III	Received Glibenclamide orally at dose of 500 mcg/kg b.w. for 14 days
Group IV	Diabetic rats received hydroalcoholic extract of *Vitex trifolia* (100 mg/kg/day p.o.)
Group V	Diabetic rats received hydroalcoholic extract of *Vitex trifolia* (200 mg/kg/day p.o.)
Group VI	Diabetic rats received hydroalcoholic extract of *Vitex negundo* (100 mg/kg/day p.o.)
Group VII	Diabetic rats received hydroalcoholic extract of *Vitex negundo* (200 mg/kg/day p.o.)
Group VIII	Diabetic rats received hydroalcoholic extract leaves of *Vitex parviflora* (100 mg/kg/day p.o.)
Group IX	Diabetic rats received hydroalcoholic extract leaves of *Vitex parviflora* (200 mg/kg/day p.o.)
Group X	Diabetic rats received phytosomal formulation (100 mg/kg/day p.o.)
Group XI	Diabetic rats received phytosomal formulation (200 mg/kg/day p.o.)

Data were analyzed by one way ANOVA, where applicable *p<0.05; **p<0.01; ***p<0.001 was considered statistically significant, compared with vehicle.

3. RESULTS

The serum glucose level of diabetic control group significantly increased compared to normal control group. The groups treated with standard drug, leaves extract and phytosomal formulation (200 mg/kg) showed significant reduction of glucose level. The highest reduction of glucose level was observed on 21th day as shown in table 1. The result of diabetic control group showed significant decrease in body weight. Whereas phytosomal formulation (200 mg/kg) and Glibenclamide treated rats were found to gain body weight, compared to diabetic control group as shown in Table 2. The animals treated with standard drug, leaves extracts and phytosomal formulation (100 and 200 mg/kg body weight), showed significant reduction in levels of triglycerides, total cholesterol, total protein and LDL in diabetic rats compared to control group and at the same time the level of HDL in the treated group showed significant increase compared to untreated control group Table 3.

Table 1. Effect of plant of *Vitex trifolia, Vitex negundo*, *Vitex parviflora* and phytosomal formulation on serum glucose level in rats

Group	**Drug and Dose**	**Serum glucose levels (mg/dl)**		
		0 Day	**8th Days**	**21th Days**
I	Normal Control (Saline)	70.24±3.82	86.63±5.32	105.36±6.38
II	Diabetic Control (STZ)	289.40±7.45	385.00±10.35	403.23±10.31
III	STZ+ Glibenclamide	260.00±6.26	130.41±7.54	109.00±5.53
IV	STZ+ *Vitex trifolia* 100 mg/kg	263.00±5.58	129±8.07	120.00±7.12
V	STZ+ *Vitex trifolia* 200 mg/kg	260.00±4.74	130.18±7.71	115.17±6.16
VI	STZ+ *Vitex negundo* 100 mg/kg	270.44±6.28	139.35±7.51	132.25±7.87
VII	STZ+ *Vitex negundo* 200 mg/kg	262.26±6.47	136.68±6.43	123.00±6.00
VIII	STZ+ *Vitex parviflora* 100 mg/kg	272.48±5.17	141.00±6.77	133.12±6.69
IX	STZ+ *Vitex parviflora* 200 mg/kg	265.38±6.96	135.31±6.11	121.16±7.1
X	Diabetic + phytosomal formulation (100 mg/kg)	263.00 ±6.42	131.00±4.58	120.17±3.51
XI	Diabetic + phytosomal formulation (200 mg/kg)	264.00±5.75	132.17±3.87	114.34±4.1

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 vs. control group respectively (One-way ANOVA followed by Dunnett's test)

Table 2. Effect of plant of *Vitex trifolia, Vitex negundo*, *Vitex parviflora* and phytosomal formulation on body weight in rats

Group	Drug and Dose	Body Weight(gm)	
		Initial weight (g)	Final weight (g)
I	Normal Control (Saline)	192.00±8.85	204.00±9.12
II	Diabetic Control (STZ)	202.5±10.42	165.00±8.78
III	STZ+ Glibenclamide	192.23±10.49	210.00±11.63
IV	STZ+ *Vitex trifolia* 100 mg/kg	175.00±10.86	209.00±10.08
V	STZ+ *Vitex trifolia* 200 mg/kg	170.00±9.79	206.00±10.37
VI	STZ+ *Vitex negundo* 100 mg/kg	198.00±8.16	216.00±10.92
VII	STZ+ *Vitex negundo* 200 mg/kg	201.40±9.60	215.00±10.41
VIII	STZ+ *Vitex parviflora* 100 mg/kg	198.56±9.33	214.26±10.79
IX	STZ+ *Vitex parviflora* 200 mg/kg	200.18±8.58	214.84±10.47
X	Diabetic + phytosomal formulation (100 mg/kg)	168.00±4.8	190.00±6.13
XI	Diabetic + phytosomal formulation (200 mg/kg)	172.00±5.45	207.00±9.21

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 vs control group respectively (One-way ANOVA followed by Dunnett's test)

Table 3. Effect of plant of *Vitex trifolia, Vitex negundo, Vitex parviflora* and phytosomal formulation on serum lipid profiles in rats

Group	Drug and Dose	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	DL (mg/dl)	LDL (mg/dl)	Total Protein (g/dl)
I	Normal Control	143.71±6.13	113.2±4.82	50.15± 3.14	77.25±6.45	5.52±4.8
II	Diabetic Control	245.46±10.34	213.47±4.35	30.21± 1.33	175.28±6.14	14.8±4.6
III	STZ+ Glibenclamide	186.22±5.28	131.1±5.62	45.18± 2.3	87.43±6.2	7.3±2.7
IV	STZ+ *Vitex trifolia* 100 mg/kg	201.13±8.44	152.65±4.39	40.94± 1.84	113.33±6.15	8.1±3.7
V	STZ+ *Vitex trifolia* 200 mg/kg	196.3±10.31	148.26±5.31	41.68±1.75	102.57±6.21	5.9±6.1
VI	STZ+ *Vitex negundo* 100 mg/kg	204.18±8.73	167.52±4.46	40.55±1.79	118.41±6.14	6.7±3.4
VII	STZ+ *Vitex negundo* 200 mg/kg	202.38±9.83	161.43±5.17	40.29±1.39	120.71±5.96	6.8±3.1
VIII	STZ+ *Vitex parviflora* 100 mg/kg	203.35±6.78	166.25±5.19	41.39±1.83	121.58±6.16	6.9±3.4
IX	STZ+ *Vitex parviflora* 200 mg/kg	200.49±9.41	162.38±4.81	40.43±1.71	113.32±5.51	7.1±5.3
X	Diabetic + phytosomal formulation (100 mg/kg)	198.83±8.1	150.16±5.65	43.50±1.66	110.15±6.41	7.2±3.15
XI	Diabetic + phytosomal formulation (200 mg/kg)	192.24±9.06	141.49±4.93	42.67±1.73	101.51±5.33	7.4±3.5

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test)

4. DISCUSSION AND CONCLUSION

In the present work the acute toxicity study that was performed to determine the LD_{50} values of leaves extracts and phytosomal formulation showed that the animals were safe up to a maximum dose of 2000 mg/kg body weight. There were no changes in normal behavior pattern and at the same time there was no mortality or no symptoms of any toxicity. In the STZ induced antidiabetic activity of leaves extracts and phytosomal formulation at dose levels of 100and 200mg/kg body weight in the result showed that there was significant reduction in blood glucose level. The results were more prominent at the dose of 200mg/kg body weight and was comparable to the group that received standard drug on 21st day (114.34 ± 4.1* and 109.00 ± 5.53* respectively). In case of change in body weight in the diabetic rats that were treated with standard drug, leaves extracts and phytosomal formulation (100 and 200 mg/kg body weight), it was observed that groups of animals treated with standard drug and phytosomal formulation recovered significantly and their body weight was regained after treatment for 21 days, which may be attributed to improved glycemic control achieved by the administration of the phytosomal formulation and the drug. Here also the results at the dose of 200 mg/kg body weight and was comparable to the group that received standard drug on 21st day. The level of lipids in the serum increases in case of type II diabetes, which is usually due to deposits of fats that results because of inactivity or insufficiency of insulin. In the present study also the diabetic rats showed hypercholesterolemia and hypertriglyceridemia.

However when the animals were treated with standard drug leaves extracts and phytosomal formulation. It was noted that the lipid, protein and triglycerides level decrease significantly and also the level of HDL increased. This implies that leaves extract and phytosomal formulation can be useful in correcting the lipid profile associated with type II diabetes [18]. This work proved that the leaves extracts and phytosomal formulation at the doses of 100 and 200 mg/kg body weight possess significant antidiabetic activity. The result also showed that total cholesterol, triglyceride, total protein, low density lipoprotein (LDL) decreases significantly and the level of HDL increased as compared to diabetic control. The result also shows that the leaves extract and phytosomal formulation has a dose dependent activity. We may conclude here that the formulation that was procured from a tribal healer possess promising activity in case of type II diabetes and can be used effectively for its management. However, further studies are required not only to identify and characterize the phytoconstituents present in the formulation that are responsible for the activity, also an in depth an exhaustive pharmacological study are required to understand the mechanism by which the formulation works for management of type II diabetes.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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