Section A -Research paper

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ANTI-DIABETIC POTENTIALS OF ENCAPSULATED *MANGIFERIN* IN STREPTOZOTOCIN INDUCED DIABETIC RAT MODEL

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ABSTRACT

In a streptozotocin-induced diabetic rat model, research is being done on the anti-diabetic potential of mangiferin. Mangiferin was given orally at doses of 200 mg/kg and 400 mg/kg, along with phytosome extracts (100 mg/kg and 200 mg/kg), and glibenclaimide (10 mg/kg), to diabetic rats caused by streptozotocin.. Diabetes-treated diabetic rats received mangiferin, which decreased blood glucose and haemoglobin levels while raising insulin and haemoglobin levels. Every parameter is operating normally. In the liver tissue of rats treated for diabetes, this activity diminished. These results showed that mangiferin has antidiabetic action in diabetic rats produced by STZ. Mangiferin's antidiabetic effects were compared to those of common antidiabetic medications.

Keywords: - *Mangiferin,* antidiabetic drug, streptozotocin

1. INTRODUCTION

Diabetes is a persistent illness. Hyperglycemia could be one of its characteristics. These could be useful in treating both insulin action and insulin secretion abnormalities. Inadequate insulin secretion and tissue size brought may result in anomalies in the metabolism of protein, carbohydrates, and lipids. These could result in modifications or elevations in blood glucose levels.

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Numerous bodily systems, including blood vessels and nerves, could be harmed by them. The survey found that between 0.5 and 3 percent of people suffered from these disorders. It has increased to about 7% these days. There are between 200 and 300 million impacted people, and in the coming years, that number should increase or triple.[1,2]

1.1 Types of diabetes

1.1.1 Type 1 diabetes mellitus (T1DM) or Juvenile Onset Diabetes

It contains 5 to 10% of population. In this type of insulin defficency immune system of the body may did not see pancreases.[3,4] For example, islets of Langerhans, blood glucose. These may produce normal glucose level and may reduce the sugar level. This is known as islet of Langerhans. Blood glucose level is use for normalized the sugar level and destruction of β- cells. This may include the antibiotic cell of islet, insulin to autoantibodies, GAD to antibodies, tyrosine phosphate and IA-2 β.[5,6]

1.1.2 Type 2 diabetes mellitus (T2DM) or Adult-Onset Diabetes

This diabetes may affect 90 to 98% of the population. This may be linked to modern style factor. This was common in adults. This may be decreased the disease condition.[7,8] This may decline the insulin action. It has heterogeneous disorder by progressive decline and inability of pancreatic beta cells of insulin resistance or dysfunction of beta cells. This disease may be associated with obesity, age older and has a history of diabetes.[9,10]

The family Anacardiaceae includes the sizable evergreen tree Mangifera indica. When the leaves are young, they are reddish and thinly flaccid, and when they are crushed, they exude an aromatic odour.[11,12] Although the fruit is a common big drupe, there is a wide range in its size and shape. It contains a single seed, a thick yellowish-red skin, and a thick yellow flesh when fully mature. The single seed is oblong or spherical and protected by a thick, fibrous endocarp.[13,14,15]

2. MATERIAL AND METHODS

2.1 Collection of material

The plants' raw materials were gathered from regional farmers in Rajasthan, India. Before extraction, plant materials were shade-dried and coarsely pulverised.

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2.2 Preparation of extract

Leaves were washed in water to remove any contamination. Then 80% ethanol was used to wash the leaves. These leaves are then placed in an oven set at 50°C for 24 to 30 hours before being pulverised into a fine powder. 200ml of solvents are used to dissolve 50gm of the samples. Keep this for 48 to 50 hours while it is 40°F outside and being shaken at 150RPM. Petroleum ether, chloroform, ethyl acetate, n-butanol, and water were the solvents employed. Once the solvent has evaporated, the sample is next transferred to a rotatory vacuum evaporator set at 400°C. These samples were then placed in a 40°C refrigerator and used for the phytochemical analysis. The sample was weighed, and stock solution was made. These answers are employed in the ensuing analysis.

2.3 *In-vivo* anti-diabetic activity

By using a method that has been previously described in the literature, the *in vivo* anti-diabetic activity was assessed. Wistar rats (weighing 160–250 g) were obtained. The animals were housed in typical polypropylene cages in a typical laboratory environment with a temperature of 30 2°C and a relative humidity of 60 65 percent. They also had access to a normal diet and an endless supply of water. *Mangifera indica* was chosen in the dosage.

2.4 Oral glucose tolerance test (OGTT)

The six animals were divided into the following six groups at random.

Group I: The control was supplied as glucose (3g/kg).

Group II: a glucose concentration of 200 mg/kg and an alcohol extract

Group III: a glucose concentration of 400 mg/kg and an alcohol extract

Group IV: obtained Hydroalcoholic Extract Phytosomes (100 mg/kg) and Glucose.

Group V: Phytosomes of Hydroalcoholic Extract in 200 mg/kg coupled with Glucose.

Group VI: got Glibenclamide together with 10 mg/kg of glucose.

Blood samples will be obtained from each group at 0, 20, 50, and 120 minutes before and after the

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administration of glucose. Blood glucose levels will be estimated using a glucometer.

2.5 Streptozotocin induced diabetic model

Animals are highly sensitive to the naturally occurring chemical streptozotocin. have created a brand-new experimental diabetic state in adult rats that, in terms of insulin sensitivity to glucose, resembles type 2 diabetes more. A dose of 200–230 mg/kg body weight. 15 minutes before the administration of 60 mg/kg of streptozotocin results in a maximum number of animals with a 40% loss in pancreatic cell mass and moderate stable non-fasting hyperglycemia (160–180 mg/dl). The streptozotocin-nicotinamide type 2 model is characterised by a mild stable hyperglycaemia, glucose intolerance, and an altered, and shares many characteristics with human type 2 diabetes. Streptozotocin (60 mg/kg), 15 minutes after the i.p. administration of extract (110 mg/kg), was used to cause diabetes in overnight fasted rats. The extract was dissolved in sterile saline, whereas streptozotocin was dissolved in citrate buffer (0.1 M, pH 4.5).

2.5.1 Experimental Protocol

Animals with diabetes were divided into the following six-animal groups at random.

Group I: diabetic management received a car (Normal saline)

Group II: Animals with diabetes were given 200 mg/kg of hydroalcoholic extract.

Group III: Animals with diabetes were given 400 mg/kg of hydroalcoholic extract.

Group IV: Animals with diabetes were given phytosomes containing 100 mg/kg of hydroalcoholic extract.

Group V: Animals with diabetes were given phytosomes containing 200 mg/kg of hydroalcoholic extract.

Group VI: Animals with diabetes were given glibenclamide (10 mg/kg).

2.5.2 Treatment

Rats that had been fasting for the previous night were used in the experiments. Fasted animals were tested to see how vehicle, extract, and conventional drugs affected their blood sugar levels and body weight at 0, 8, 15, and 28 days following oral treatment. All animals were given a retro-orbital plexus and cardiac puncture at the 21st day under a light anaesthetic, and blood samples were taken.

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2.6 Biochemical parameters

All animals had blood drawn using the retro-orbital plexus technique, which was then centrifuged at 3000 rpm for 20 minutes. The separated serum was kept at -20°C until analysis was done. Using the diagnostic kit in the Autoanalyzer, serum samples were examined for cholesterol, HDL, LDL, VLDL cholesterol, total proteins, urea, creatinine, and triglycerides.

2.6.1 Effect on Body weight

Animals were weighed at 0, 8, 15, and 28 days during the 28-day trial period to determine the effects of the vehicle, standard medication, and all solvent fractions on body weight.

2.6.2 Methods for estimation of biochemical parameters

2.6.2.1 Collection of Blood and separation of Serum

Cardiovascular puncture and the retro-orbital plexus technique were used. It was centrifuged at 3000 rpm for 20 min. Supernatant of the isolated serum was kept at -20°C until analysis was done.

2.6.2.1.1 Determination of serum cholesterol

Mix well incubate at 37°C for 10 min and analyzed in an autoanalyzer against blank.

Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled water	10 µl	-	-
Standard	-	10 µl	-
Sample	-	-	10 µl

Table 1. Assay procedure

2.6.2.1.2 Determination of HDL level

Phosphotungstate is used to precipitate LDL and VLDL (low and very low-density lipoproteins) from serum in the presence of divalent cations. Using the ERBA Cholesterol Reagent, the HDL cholesterol in the supernatant is determined while being unaffected.

10 minutes of well-mixed incubation at 37 °C. Using an auto-analyzer and a reagent blank, measure each sample's and the standard's absorbance at 505 nm.

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Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled water	60 µl	-	-
Standard	-	60 µl	-
Sample	-	-	60 µl

Table 2. Assay procedure

2.6.2.1.3 Determination of VLDL level

VLDL cholesterol was calculated by deduction of the sum of the cholesterol fractions from the total cholesterol serum concentration

2.6.2.1.4 Determination of LDL cholesterol

LDL = Total cholesterol – [TG/5 + HDL cholesterol]

TG/5 = VLDL

2.6.2.1.5 Determination of Triglycerides level

Stir and let sit for 10 minutes at 37 °C. Using an automatic analyzer and a reagent blank, absorbance at 510 nm.

Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled water	20 µl	-	-
Standard	-	20 µl	-
Sample	-	-	20 µl

Table 3. Assay procedure

2.6.2.1.6 Determination of serum Creatinine

Stir thoroughly, then incubate for 10 minutes at 37 °C. In an auto-analyzer, compare the absorbance of the standard and each sample to the reagent blank.

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2.6.2.1.7 Determination of serum Urea

Stir thoroughly, then incubate for 10 minutes at 37 °C. In an auto-analyzer, compare the absorbance with sample.

Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled water	30 µl	-	-
Standard	-	30 µl	-
Sample	-	-	30 µl

Table 4. Assay procedure

2.6.2.1.8 Determination of Total protein

10 minutes of well-aerated incubation at 37 °C. Check each sample's and the standard's absorbance in an auto-analyzer against a reagent blank.

Pipette into tubes marked	Blank	Standard	Sample
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled water	40 µl	-	-
Standard	-	40 µl	-
Sample	-	-	40 µl

Table 5. Assay procedure

2.7 Histopathology

Histology is the study of the tiny anatomy of plant and animal cells and tissues. It is carried out by looking at a little piece of tissue under a light or electron microscope. The field of biology known as histology is concerned with the investigation of the microscopic organisation of cells and tissues in both plants and animals. All types of animals were anaesthetized. The prepared slides were then examined, and photos were taken using a binocular microscope equipped with a camera.

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2.8 Stability Studies

After six months of storage, the formulation's physical stability was examined under three different conditions: ambient (room temperature), accelerated (40 2°C/75 5 percent RH), and refrigerated (by maintaining the same at (2-8°C)). At all three temperatures, formulations were kept in tightly closed glass bottles.

3. RESULT AND DISCUSSION

3.1 Anti-diabetic effect in vivo

3.1.1 Oral glucose tolerance test (OGTT)

3.1.1.1 OGTT of optimized formulation of *Mangifera indica*

Within 30 minutes of the glucose tolerance test starting, the blood glucose levels had virtually doubled from their initial level of control. Before the hyperglycemia began to decrease, it remained for 60 minutes. Mangifera indica effectively lowered the rise in blood glucose levels that happened 60 minutes after glucose infusion at dosages of 200 and 400 mg/kg. After 60 minutes, Mangifera indica phytosomes halted the rise in blood sugar levels. Additionally, glibenclamide stopped the rise in blood glucose levels after 30 minutes.

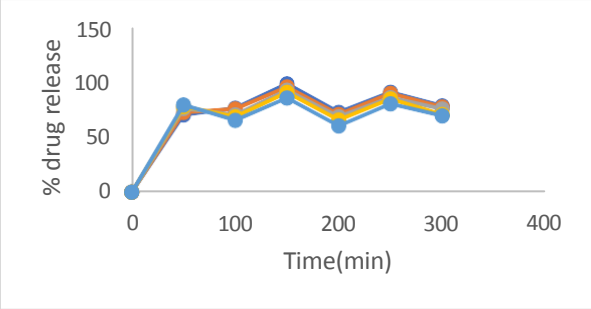

Figure 1. Oral glucose tolerance test using an improved Mangifera indica formulation

3.2 Streptozotocin Induced Diabetic Model

3.2.1 STZ model for plant extracts

3.2.1.1 Effects of phytosomes extract, glibenclaimide, and plant extracts on the rats with diabetes induced by streptozocin's serum glucose levels

The impact of glibenclaimide (10 mg/kg), phytosome extracts (100 and 200 mg/kg), and extracts (200 and 400 mg/kg) throughout the course of a 21-day period on the amount of serum glucose in

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diabetic rats brought on by streptozotocin. For 21 days, the dose was given orally to the animals once daily. Blood samples were taken after 21 days via the retro-orbital plexus while being lightly sedated. But in the diabetes therapy groups, the serum glucose level consistently and progressively dropped.

Figure 2. Serum glucose levels in diabetic rats caused by streptozotocin

3.2.1.2 Effect of plant extracts, phytosomes *Mangifera indica* and glibenclaimide on the levels of HDL-C, VLDL-C, LDL-C, and serum triglycerides in streptozotocin-induced diabetic rats.

Following a 21-day course of therapy, diabetic rats received dosages of 100 mg/kg and 200 mg/kg showed significantly decreased blood triglyceride, VLDL-C, LDL-C, and cholesterol levels, as well as higher HDL-C levels. In addition, the common medication glibenclaimide (10mg/kg) shown a reduction in blood triglycerides, VLDLC, and LDL-C as well as an increase in HDL-C levels in comparison to the control group.

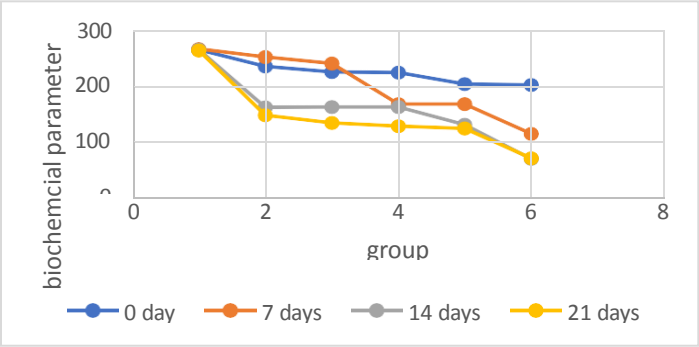

Figure 3. The effects of plant extract, Mangifera indica phytosomes, and glibenclamide were

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investigated on the blood cholesterol, triglyceride, HDL-C, VLDL-C, and LDL-C levels in streptozotocin-induced diabetic rats.

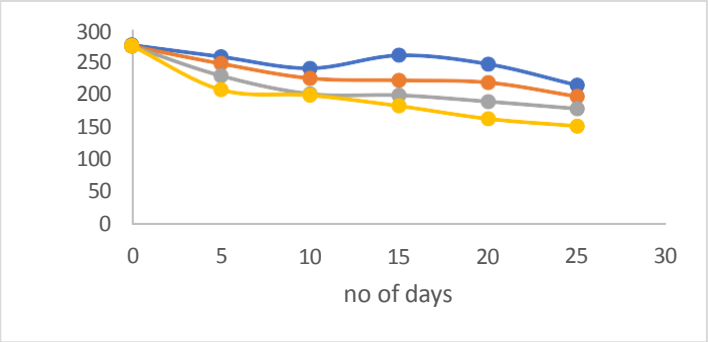

Figure 4. Effect of extract, phytosome of *Mangifera indica* and glibenclaimide on serum glucose level

3.2.1.3 Effect of plant extract, phytosomes of *Mangifera indica* and glibenclaimide on urea, creatinine, and protein in streptozotocin induced diabetic rats

The normal treatment, extracts, and phytosomes decreased the serum concentrations of urea and creatinine in a dose-related manner, but had the opposite effect on the serum concentration.

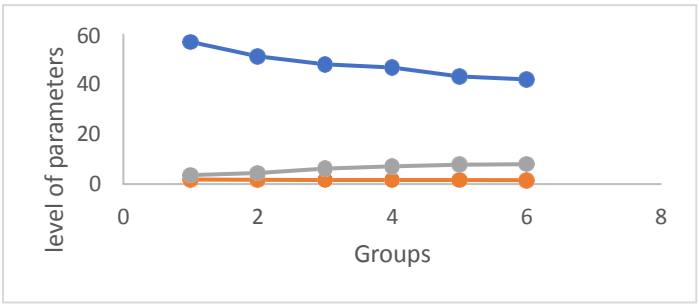

Figure 5. Effect of plant extract, phytosomes of *Mangifera indica* and glibenclaimide on urea, creatinine, and protein in streptozotocin induced diabetic rats

3.2.1.4 Effect of plant extracts, phytosome of *Mangifera indica* and glibenclaimide on body weight in streptozotocin induced diabetic rats

Mangifera indica, its phytosome, and glibenclaimide's effects on body weight in rats with streptozocin-induced diabetes. Body weight loss in the untreated diabetic rat correlates with protein degradation and fat catabolism and may be brought on by a lack of glucose for calorie consumption. However, diabetic rats receiving treatment had considerably (p0.05) lower body

eight

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weights. The diabetic rat's body weight increased progressively and steadily with glibenclaimide (10 mg/kg).

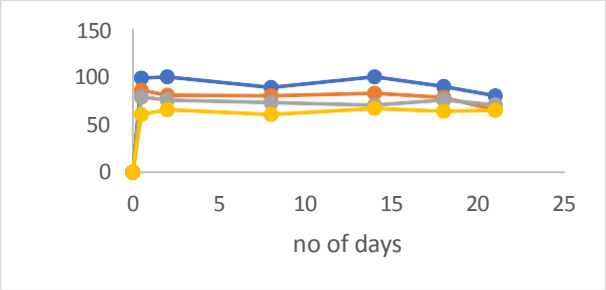

Figure 6. Effect of plant extract, phytosomes of *Mangifera indica* and glibenclaimide on body weight

3.3 Histopathological examination

3.3.1 Histopathological examination after treatment

Microscopic analysis revealed severe islet vacuolation, necrotic alterations, degranulation, and collapse of the pancreatic beta-cell architecture. There were discovered to be fewer and smaller pancreatic islets. The architecture of the pancreatic islets, as well as the amount of fibrosepta and the pattern of the islets, improved in groups II and III, which respectively received Mangifera indica at different doses. The recovery of -cells began, cell proliferation took place, vacuolation was reduced, and the quantity and size of pancreatic islets were discovered to have increased in group IV and V, which received an optimized Phytosomal formulation (Mangifera indica) at doses of 100 mg/kg and 200 mg/kg. The anatomical structure of the islets significantly improved in the group VI that received glibenclaimide treatment. Vacuolation did not occur, and new -cells were formed. The glomeruli and renal convoluted tubules of the untreated diabetic rats' kidneys exhibited a variety of pathological alterations; there was a mild hypertrophy, dilatation, and congestion of glomerular. A heterogeneous eosinophilic substance filled the proximal convoluted tubules, and glomerular damage-related haemorrhages were also present in the Bowman's space. Following treatment, these alterations returned to their original state.

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1. Histopathology study of pancreases

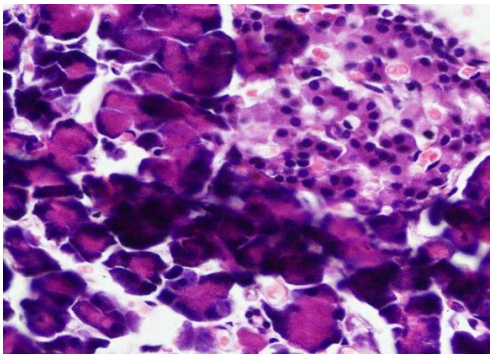

Figure 7. Diabetic control

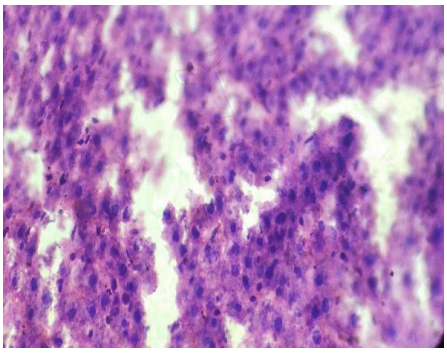

Figure 8. *Mangifera indica* dose 200mg/kg

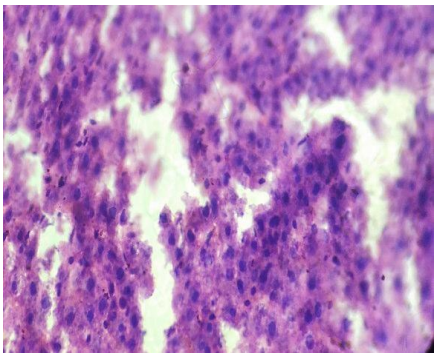

Figure 9. *Mangifera indica* dose 400 mg/kg

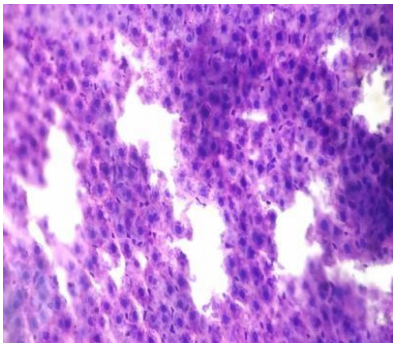

Figure 10. Optimized formulation 100mg/kg

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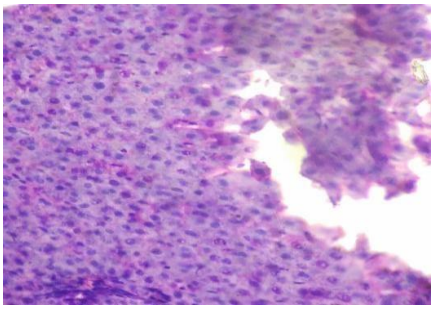

Figure 11. Optimized formulation dose 200mg/kg

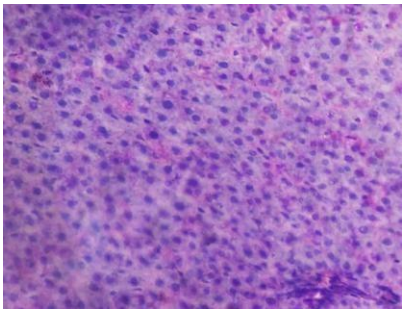

Figure 12. Standard drug

2. Histopathology study of Kidney

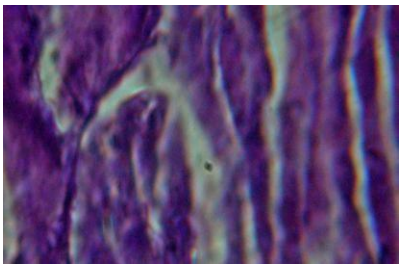

Figure 13. Diabetic control

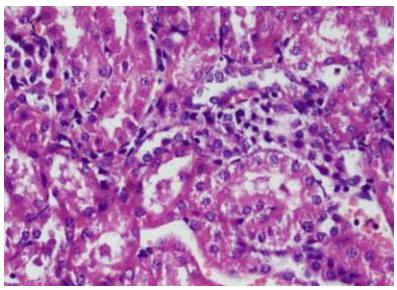

Figure 14. *Mangifera indica* dose 200mg/kg

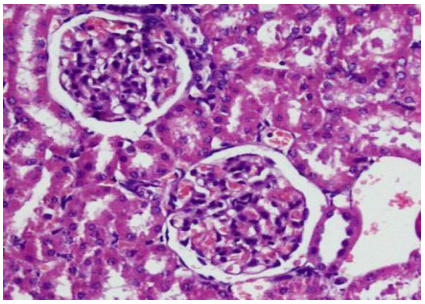

Figure 15. *Mangifera indica* dose 400 mg/kg

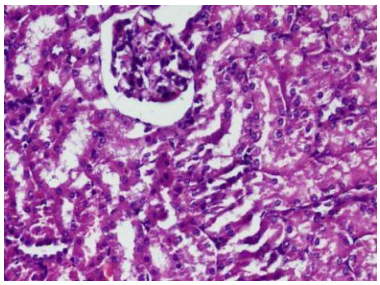

Figure 16. Optimized formulation dose 100mg/kg,

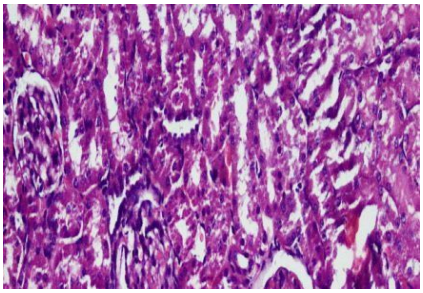

Figure 17. Optimized formulation dose 200mg/kg

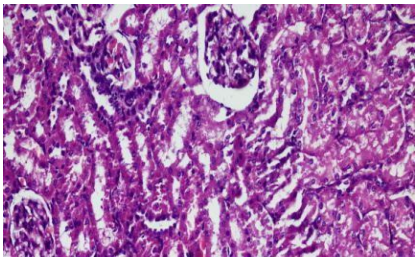

Figure 18. Standard drug

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3.4 Stability Studies

Until the formulation reaches the desired tissue, stability must be maintained. Due to cholesterol's capacity to make the lipid bilayer flexible, the physical stability is crucially maintained. Cholesterol and soy lecithin have an interaction that strengthens the electrostatic attraction between phospholipid bilayers, ultimately leading to enhanced stability. A stability analysis for particle size, span, and entrapment efficiency was performed at 0, 1, 3, and 6 months. The impact of the stability research on the span and entrapment efficiency at 0, 1, 3, and 6 months after storage under three different conditions: ambient temperature (room temperature), accelerated condition (40 20C/75 5 percent RH), and refrigerated condition (2-80C). Particle size, span, and entrapment effectiveness at refrigerated conditions were unchanged even after 6 months.

Stability condition	**Mean particle size(nm)**			
	0month	**1 month**	**3month**	**6month**
2-8^{0}C	223 ± 0.55	224 ± 0.51	240.25 ± 0.42	243.75 ± 0.62
Room temperature	223 ± 0.55	224.96 ± 0.21	240.25 ± 0.42	243.45 ± 0.61
40 ± 2^{0}C/75 ± 5% RH	223 ± 0.55	224.45 ± 0.61	240.25 ± 0.41	243.45 ± 0.70

Table 6. Effect of storage time for optimum formulation on mean particle size

Stability condition	**Span**			
	0month	**1 month**	**3month**	**6month**
2-8^{0}C	0.41 ± 0.21	0.41 ± 0.32	0.41 ± 0.30	0.41 ± 0.31
Room temperature	0.41 ± 0.21	0.47 ± 0.33	0.42 ± 0.30	0.43 ± 0.41
40 ± 2^{0}C/75 ± 5% RH	0.41 ± 0.21	0.47 ± 0.25	0.42 ± 0.31	0.43 ± 0.42

Table 7. Effect of storage time on formulation's formulation span

Stability condition	**Entrapment efficiency**			
	0 month	**1 month**	**3month**	**6month**
2-8^{0}C	62.2 ± 0.31	62.2 ± 1.42	62.2 ± 1.23	62.2 ± 1.32
Room temperature	62.2 ± 0.31	65.3 ± 1.52	65.3 ± 1.42	64.3 ± 1.56
40 ± 2^{0}C/75 ± 5% RH	62.2 ± 0.31	65.2 ± 0.41	66.3 ± 0.45	70.2 ± 0.65

Table 8. Effect of storage time on the effectiveness of entrapment for an optimal formulation

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4. SUMMARY

By using an in vivo model, the anti-diabetic effects of extracts and phytosomes were compared. For the purpose of comparing the antidiabetic activity of extracts and phytosomes, the OGTT (Oral Glucose Tolerance Test) and STZ diabetic model were used. This hyperglycemia persisted for 60 minutes before beginning to decline. At doses of 200 and 400 mg/kg, Mangifera indica prevented the rise in blood glucose levels that occurred 60 minutes after glucose injection. After 60 minutes, phytosomes prevented the blood glucose from rising. Additionally, after 30 minutes, glibenclamide prevented the rise in blood glucose levels. Plant extract reduced serum glucose levels in a STZ-induced diabetes mouse by 17% and 19% at doses of 200 mg/kg and 400 mg/kg, respectively. At doses of 100 mg/kg and 200 mg/kg in comparison to this optimised phytosomal formulation, serum glucose levels were reduced by 30% and 34%, respectively, indicating increased antidiabetic action. Mangifera indica reduced serum glucose levels in a STZ-induced diabetes mouse by 33% and 39% at doses of 200 mg/kg and 400 mg/kg, respectively. The serum glucose level was reduced by 39 and 42 percent, respectively, in contrast to this improved phytosomal formulation at doses of 100 mg/kg and 200 mg/kg, indicating an improvement in therapeutic efficacy. When compared to the first day of treatment, the diabetic control group receiving no medication treatment showed a substantial drop in body weight after 21 days of treatment. The untreated diabetic rat's body weight loss correlates with protein waste and fat catabolism, and it may be caused by a shortage of glucose for use as an energy source. The body weight of the diabetic rat, however, was significantly reduced after treatment. The body weight of the diabetic rat with glibenclaimide (10 mg/kg) increased gradually and consistently. In streptozotocin-induced diabetic rats, a good effect on lipid profile was also seen, i.e., a decrease in serum concentration of cholesterol, triglycerides, LDL, and VLDL and an increase in HDL level, indicating its hypolipidemic action. The serum concentrations of urea and creatinine were reduced in a dose-related manner by the usual medication, extracts, and phytosomes, whereas the serum concentration of total protein was affected in the opposite way.

The kidney and pancreas benefit from both phytosomal formulations, according to the histopathological examinations. The transformation of these essential organs from diabetic state to

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normal state was facilitated by optimised phytosomal production. In diabetic rats, there was significant damage to the islets of Langerhans and a reduction in their size. The normal cellular population had been partially recovered thanks to phytosomes. In diabetic rats, the mesangium density and the basement membrane of the glomeruli's arterioles both mildly changed in thickness. These alterations were brought back to normal after receiving therapy with phytosomal formulation.

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