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# Assesment of Antidiabetic Activity of *Mangifera Indica* Seed Kernel Extracts in Streptozotocin Induced Diabetic Rats

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## Abstract

The objective of the study was to screen the extracts of *Mangifera indica* seed kernel for its antidiabetic activity so that tons of mango seed kernels going waste during the mango season can be utilized as house hold remedy in treating diabetes so that the dose and cost of the actual treatment can be brought down. Extracts were evaluated for their glucose reducing effect in both normal and diabetic rats at the dose of 200 mg/kg body weight. Diabetes was induced by administering streptozotocin at 65 mg/kg body weight in citrate buffer intraperitonially. Blood samples were collected through tip of tail vein and the fasting blood glucose levels were estimated by using reactive strips of glucose oxidase and peroxidase. Serum lipid profiles were carried out by using ready kits by colorimetric method. The results indicate aqueous and methanolic extract of *Mangifera indica* seed kernel possesses significant antidiabetic activity.

**Keywords:** *Mangifera indica*, Seed kernel, Streptozotocin, Anti-hyperglycaemic activity

## 1. Introduction

Diabetes mellitus is a chronic disease characterized by high blood glucose levels due to absolute or relative deficiency of circulating insulin levels [1]. The objective of the study was to screen the extracts of *Mangifera indica* seed kernel for its antidiabetic activity so that huge resource of mango seed kernel going waste during the mango season can be utilized as house hold remedy against diabetes so that the dose and cost of the actual treatment can be brought down. In spite of treating diabetes mellitus mango seed kernel can also be used as preventive house hold remedy against many diseases since it is a potent antimicrobial and antioxidant. Many unknown and lesser known plants are used in folk and tribal medicinal practices in India [2]. The medicinal values of these plants are not known much to the scientific world. The seed kernel of *Mangifera indica* (Aam, Mangai, Mavu, Am, Amba) is one such herbal source which is mentioned in Ayurveda for treating diabetes mellitus. However in Nigerian folk [3] the leaves of *Mangifera indica* are used in the treatment of diabetes mellitus by the local people. The seed kernel is sweet, acrid, astringent, refrigerant, anthelmintic, constipation, haemostatic and uterine tonic. It is useful in vitiated conditions of pitta and kapha, helminthiasis, chronic diarrhoea, dysentery, hemorrhages, haemoptysis, haemorrhoids, ulcers, bruises, leucorrhoea, menorrhagia, diabetes, heartburn and vomiting [4]. Various pharmacological studies have been conducted and reported so far using different parts of *Mangifera indica*. Anti inflammatory, anti oxidant and antimicrobial activities of the seed kernel of *Mangifera indica* [5] has been reported. Diabetes is considered to be a silent killer and nearly 10% of the Indian population is affected. It is estimated that nearly 15% of the population will be affected by 2015 [6]. Probably the highest affected

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population in the world. An attempt was made to screen the antidiabetic potential of *Mangifera indica* seed kernel extracts.

## 2. Materials and Methods

### 2.1 Plant Material and Extraction

*Mangifera indica* (fam. Aanacardiaceae) is a widely cultivated and large spreading evergreen tree distributed throughout India up to 1200 m altitude. *Mangifera indica* seed kernel was collected during mango season in the month of December January from the fruits market in Bangalore. It was identified and authenticated by Dr. Siddamalaiah, Regional research centre, Bangalore. Shade-dried powdered seed kernel (5 kg) of *Mangifera indica* was extracted with Pet Ether, chloroform, methanol and distilled water by soxhletting until the solvents were clear. The extracts were evaporated and solvents were recovered using solvent recovery condenser except water. The yields of the extracts were 2, 3, 9 and 5 percent respectively and were semisolid in nature.

### 2.2 Experimental Animals

Adult male Wistar rats weighing 175–200 g of age 3 to 4 months and adult female mice (for acute toxicity studies) of age 8 to 12 weeks old were used in the present study. Animals were obtained from Drugs Testing Laboratory, Palace Road, Bangalore. They were acclimatized to the laboratory conditions for 5 days before experimentation. The animals had free access to food and water and were housed under a natural light-dark cycle. The experiment was carried out with the approval of the Institutional Animal Ethics Committee (Proposal No. GCP/CPCSEA/IAEC/2009–10).

#### *2.2.1 Acute toxicity study*

Acute toxicity study was conducted as per guidance for Industry. Single Dose Acute Toxicity Testing for Pharmaceuticals (OECD guidelines 425), to determine acute oral toxicity, *Mangifera indica* seed kernel extracts suspended in 5% Tween 80 were administered to 2 mice for each extract. Control mice received 5% Tween 80. The animals were observed continuously for the initial 4 h and intermittently for the next 6 h and then again at 24 h and 48 h following drug administration. Mortality and general behaviour of the animals were observed periodically for 48 h. The parameters observed were grooming, hyperactivity, sedation, loss of righting reflex, respiratory rate and convulsion. All the extracts were found nontoxic till 2 g/Kg body weight. One tenth of the nontoxic dose was considered as therapeutic dose.

#### *2.2.2 Induction of diabetes*

Diabetes was induced by a single Intraperitonial injection of freshly prepared streptozotocin [7] (STZ) (Sigma-Aldrich Co., St. Louis, MO, USA.) at the dose of 65 mg/kg in 0.01 M sodium citrate buffer (pH 4.5) to a group of overnight fasted rats. Diabetes was confirmed in STZ rats by measuring the fasting blood glucose concentration on fourth day after streptozotocin administration. The animals were given feed *ad libitum* and 5% dextrose solution for the next 24 hrs to overcome initial hypoglycemic phase. Depending on the Blood Glucose Levels (BGLs) the diabetic animals, 250–400mg/dl, were selected for the further study.

## 3. Experimental Design

### 3.1 Effect of Extracts on Hypoglycaemic Activity in Normal Rats

Overnight fasted male Wistar rats were divided into six groups of six animals each. Group I serving as control, received vehicle (5% Tween 80). Group II, III, IV & V received Pet Ether, Chloroform, Methanolic and Aqueous extracts orally in doses of 200 mg/kg b.w., respectively. Group VI served as reference standard and received Glibenclamide (2 mg/kg). Fasting Blood Glucose (FBG) was recorded initially and then blood samples were collected from the tail vein [8] at 30, 60, 90 and 120 min after administering the extracts. The BGL was measured by using Electronic Digital Glucometer [9] (Ascensia Entrust Blood Glucose Meter, Bayer Diagnostics India Ltd).

### 3.2 Effect of Extracts on Oral Glucose Tolerance

To perform glucose tolerance test, overnight fasted normal healthy rats were used. Rats were divided into six groups, each of six animals. Group I serving as control, received vehicle (5% Tween 80). Group II, III, IV & V received Pet Ether, Chloroform, Methanolic

and Aqueous extracts orally in doses of 200 mg/kg b.w., respectively. Group VI served as reference standard and received Glibenclamide (2 mg/kg). All the animals were given glucose 3 g/kg p.o. [10] 30 min after dosing. Blood glucose levels measured by using glucometer at 0, 30, 60, 90 and 120 min after drug administration.

### 3.3 Effect of Extracts on STZ Induced Hyperglycaemia

#### *3.3.1 Acute treatment*

Overnight fasted diabetic male wistar rats were divided into seven groups of six animals each. Group I served as normal control received vehicle (5% Tween 80). Group II served as diabetic control and received vehicle Group III, IV, V & VI received Pet Ether, Chloroform, Methanolic and Aqueous extracts orally in doses of 200 mg/kg b.w., respectively, Group VII served as reference standard received Glibenclamide (2 mg/kg). FBG test was conducted initially and then blood samples were collected at 30, 60, 90 and 120 min from tail vein after oral administration of various treatments.

#### *3.3.2 Sub Acute treatment*

Long term study of 21 days was conducted in diabetic rats. Overnight fasted diabetic male Wister rats were divided into seven groups of six animals each. Group I serving as normal control received vehicle (5% Tween 80). Group II served as diabetic control and received vehicle Group III, IV, V & VI received Pet Ether, Chloroform, Methanolic and Aqueous extracts orally in doses of 200 mg/kg b.w., respectively, Group VII served as reference standard received Glibenclamide (2 mg/kg). Blood samples were collected from tail vein of overnight fasted animals on day 1, 7, 14 and day 21 to check blood glucose levels. Total cholesterol and triglycerides were estimated from the serum samples through Semi auto analyzer of Glaxo Qualigens Co., using commercially available direct estimation kits from Team Diagnostics Pvt. Ltd. The animals were sacrificed on last day (Day 21) by euthanesia and further investigations were carried out.

#### *3.3.3 Statistical analysis*

Results were expressed as mean ± SEM. The data was evaluated by one-way ANOVA followed by Dunnet's test using Graph Pad Prism (Graph pad Software, San Diego, CA, USA). Values of $p<0.05$ were considered statistically significant.

## 4. Results and Discussion

### 4.1 Effect of Extracts on Blood Glucose Levels in Normal Rats (Table 1, Fig. 1, Fig. 1a)

The effects of aqueous extract, Pet ether extract and Methanolic extract on BGL were not significant throughout the observation period. At few intervals compared to 0 min the animals have shown marginal increase in BGL. In chloroform extract treated group the animals have shown significant ($p<0.05$) decrease in BGL at 240 min after the administration of extract. The Glibenclamide treated group of animals have shown statistically significant ($p<0.01$) fall in BGL during the observation period. However the hypoglycaemic effects produced by all the extracts are incomparable to that of the standard drug. Control or vehicle treated group did

**Table 1:** Hypoglycemic effects in normal rats

| | | | Blood Glucose Levels mg/dl | | | | |
|---|---|---|---|---|---|---|---|
| Groups | Treatments | Dose | 0 min | 30 min | 60 min | 120 min | 240 min |
| Group 1 | Vehicle, 5% Tween 80 | 5 ml/kg | 73.8 ± 2.30 | 74.6 ± 4.18 | 65.6 ± 3.37 | 70.2 ± 3.39 | 78.0 ± 2.58 |
| Group 2 | Pet Ether extract | 200 mg/kg | 72.0 ± 5.71 | 82.4 ± 3.67 | 73.0 ± 3.28 | 66.4 ± 2.99 | 72.2 ± 1.89 |
| Group 3 | Chloroform extract | 200 mg/kg | 83.2 ± 2.64 | 72.4 ± 3.98 | 71.6 ± 2.55 | 72.0 ± 2.30 | 64.4 ± 1.82* |
| Group 4 | Methanolic extract | 200 mg/kg | 73.8 ± 3.08 | 72.0 ± 4.20 | 68.8 ± 2.24 | 75.2 ± 2.19 | 70.0 ± 1.86 |
| Group 5 | Aqueous extract | 200 mg/kg | 64.8 ± 2.34 | 66.2 ± 7.18 | 68.2 ± 1.27 | 67.4 ± 2.51 | 73.4 ± 2.93 |
| Group 6 | Glibenclamide | 2 mg/kg | 72.4 ± 1.40 | 62.6 ± 2.52* | 60.8 ± 4.54* | 53.8 ± 3.61** | 62.8 ± 1.90* |

Values are Mean ± S.E; n=5, ONE-Way: ANOVA **p<0.01, *p<0.05.

Posttest: Dunnet's, compared all readings to normal control

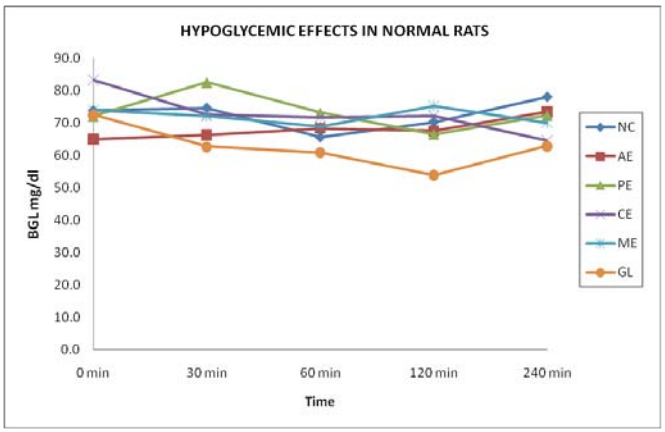


**Fig. 1.** Hypoglycemic effects in normal rats.

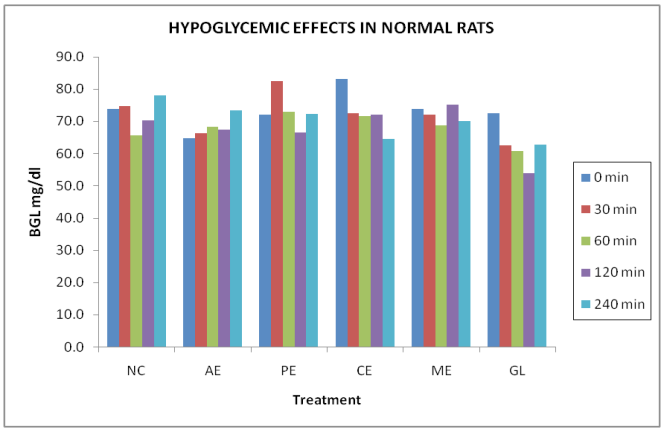


**Fig. 1a.** Hypoglycemic effects in normal rats.

not show any significant changes in the BGL throughout the observation period.

### 4.2 Effect of Extracts on Oral Glucose Tolerance Test (Table 2, Fig. 2, Fig. 2a)

Aqueous extract and Methanolic extract has shown significant decrease in blood glucose level and also there is no considerable increase in the BGL after the administration of glucose load. This may be due to the inhibition of the glucose absorption. Pet ether extract and chloroform treated groups have shown slight increase in BGL and the values at 240 min also shows slightly more than the 0 min reading but not significant. Glibenclamide treated group has shown decreased BGL even after the administration of glucose except at 60 min. Glucose loaded animals have shown gradual increase in blood sugar level at various interval of time witnessing the absorption of the glucose administered.

### 4.3 Effect on Fasting Blood Glucose Level of STZ Induced Diabetic Rats (Acute Study)

Acute effects of the extracts in overnight fasted diabetic rats are presented in Table 3, Fig. 3, and Fig. 3a. Blood glucose level (BGL) of rats of Group 1 was compared with BGL of other rats to confirm that STZ has induced diabetes in experimental animals ($p<0.01$) at all intervals of sampling. It was noticed that all the extracts of *Mangifera indica* resulted in reduction of BGL significantly except pet ether extract. Aqueous extract and methanolic extracts were significantly ($p<0.01$) effective in reducing initial BGL of 387 to 120 mg/dl and 303 to 161 mg/dl respectively, which was on par with Glibenclamide that reduced BGL from 337 to 125 mg/dl at the end of 240 minutes.

### 4.4 Effect on Blood Glucose Level and other Parameters of STZ Induced Diabetic Rats (Sub Acute Study)

The changes in BGL and body weight are reported in Table 4 (readings before and after treatment) and changes in serum lipid profile are reported in Table 5. There was a significant ($p < 0.01$) reduction in body weight in all diabetic rats within 21 days ranging from 14.7 to 27.4%. Significant ($p < 0.01$) decrease in BGL was observed in rats treated with aqueous extract and methanolic extracts which was on par with Glibenclamide in reducing the BGL from 342 to 126 mg/dl and 337 to 91 mg/dl respectively. The chloroform extract and pet ether extract were not significant. These results suggested that aqueous extract and methanolic extract of *M. indica* are better than other extracts and equivalent to the control drug Glibenclamide.

## 5. Lipid Profiles: (Table 5)

Lipid profiles of all treated groups were compared with diabetic control animals. The triglyceride levels of animals which were treated with all extracts have come down significantly compared to diabetic control group, while Glibenclamide treated group animals have shown

**Table 2:** Oral glucose tolerance test in normal animals

| Groups | Treatments | Dose | Blood Glucose Levels mg/dl | | | | |
|---|---|---|---|---|---|---|---|
| | | | 0 min | 30 min | 60 min | 120 min | 240 min |
| Group 1 | Vehicle, 5% Tween 80 + Glucose | 5 ml/kg | 60.0 ± 3.43 | 77.4 ± 4.06 | 66.6 ± 2.63 | 70.2 ± 3.74 | 69.4 ± 3.99 |
| Group 2 | Pet Ether extract + Glucose | 200 mg/kg | 62.6 ± 1.72 | 79.0 ± 3.77 | 69.0 ± 1.63 | 63.8 ± 3.89 | 63.6 ± 2.54 |
| Group 3 | Chloroform extract + Glucose | 200 mg/kg | 73.6 ± 2.45 | 84.3 ± 3.74 | 85.3 ± 5.64 | 76.8 ± 3.75 | 77.0 ± 1.84 |
| Group 4 | Methanolic extract + Glucose | 200 mg/kg | 70.2 ± 2.77 | 83.8 ± 1.40 | 81.8 ± 1.62 | 88.0 ± 2.11 | 71.4 ± 4.22 |
| Group 5 | Aqueous extract + Glucose | 200 mg/kg | 85.6 ± 2.39 | 74.6 ± 4.45 | 69.2 ± 2.14 | 75.4 ± 1.52 | 77.8 ± 2.66 |
| Group 6 | Glibenclamide + Glucose | 2 mg/kg | 64.6 ± 4.45 | 61.8 ± 2.59 | 66.1 ± 1.74 | 58.0 ± 2.72 | 63.6 ± 2.38 |

Values are Mean ± S.E; n=5, ONE-Way: ANOVA **p<0.01, *p<0.05, NS; Not significant vs. group 1.

Posttest: Dunnet's compared all readings to normal control, *significant p<0.05, **significant p<0.01, ***significant p<0.001 (extremely significant)

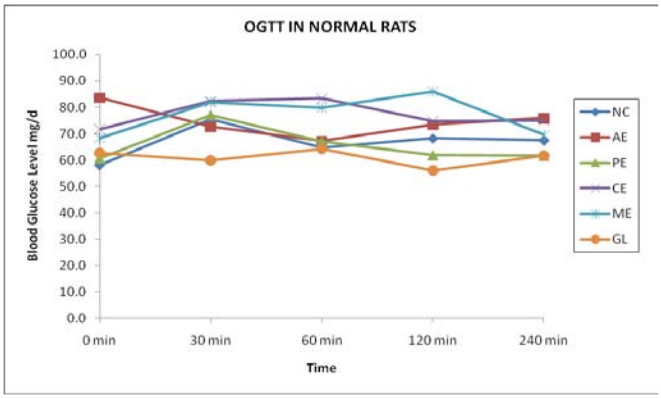


**Fig. 2.** OGTT in Normal Rats.

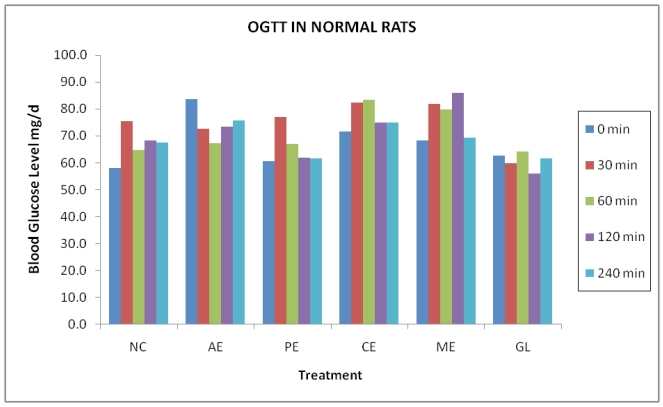


**Fig. 2a.** OGTT in Normal Rats.

**Table 3:** Hypoglycemic effects in STZ induced diabetic rats

| Groups | Treatment | Dose | Blood Glucose Levels mg/dl | | | | |
|---|---|---|---|---|---|---|---|
| | | | 0 min | 30 min | 60 min | 120 min | 240 min |
| Group 1 | Vehicle, 5% Tween 80 | 5 ml/kg | 65.5 ± 4.80 | 58.5 ± 4.06 | 65.75 ± 1.62 | 58.75 ± 2.57 | 61.25 ± 1.77 |
| Group 2 | Pet Ether extract | 200 mg/kg | 355.0 ± 46.41 | 347.5 ± 39.7 | 335.3 ± 26.59 | 351.0 ± 31.91 | 357.0 ± 32.35NS |
| Group 3 | Chloroform extract | 200 mg/kg | 348.0 ± 46.1 | 310.5 ± 36.4 | 290.5 ± 17.74 | 306.5 ± 29.62 | 250.3 ± 41.49** |
| Group 4 | Methanolic extract | 200 mg/kg | 303.0 ± 33.1 | 244.5 ± 34.8** | 247.5 ± 30.35** | 207.3 ± 34.61** | 160.5 ± 31.92*** |
| Group 5 | Aqueous extract | 200 mg/kg | 387.3 ± 43.74 | 220.3 ± 40.96** | 181.3 ± 39.95** | 155.3 ± 38.28** | 119.5 ± 44.96*** |
| Group 6 | Glibenclamide | 2 mg/kg | 336.8 ± 50.86 | 221.0 ± 43.51** | 193.5 ± 29.67** | 138.3 ± 16.4** | 125.3 ± 38.5*** |
| Group 7 | Diabetic control | 5 ml/kg vehicle | 420.0 ± 32.1 | 428.3 ± 24.03 | 431.0 ± 20.57 | 426.0 ± 4.34 | 429.3 ± 7.58 |

Values are Mean ± S.E; n=5, ONE-Way: ANOVA **p<0.01, *p<0.05, NS; Not significant vs group 7.

Posttest: Dunnet's compared all readings to 0 minute, *significant p<0.05, **significant p<0.01, ***significant p<0.001

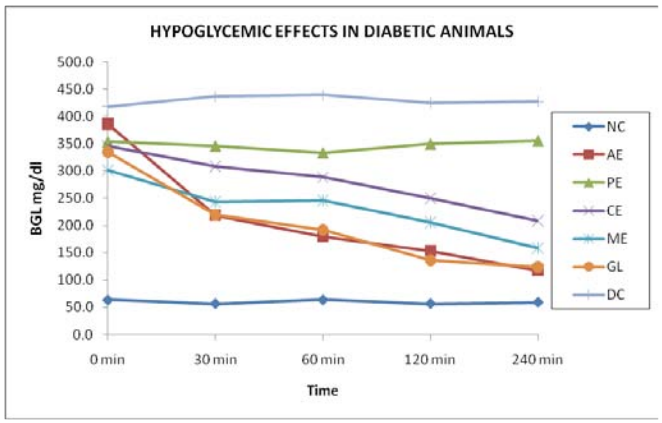


**Fig. 3.** Hypoglycemic effects in diabetic animals.

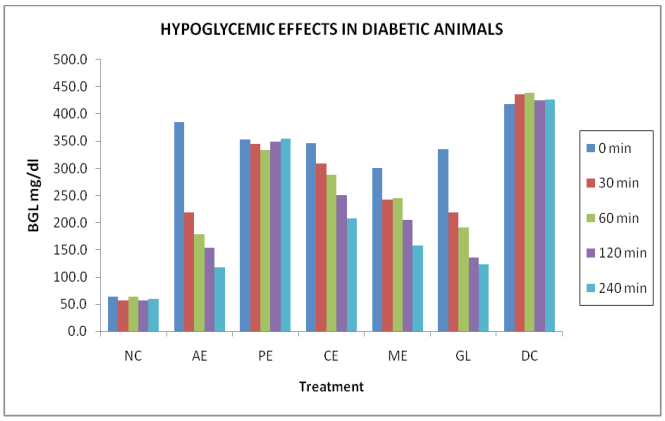


**Fig. 3a.** Hypogycemic effects in diabetic animals.

**Table 4:** Hypoglycemic studies on STZ induced diabetic rats (Sub Acute treatment)

| Groups | Treatment | Blood Glucose Level mg/dl | | | Body Weight | | |
|---|---|---|---|---|---|---|---|
| | | Before Treatment | After Treatment | % Change | Before Treatment | After Treatment | % Change |
| Group 1 | Vehicle,5% Tween 80 | 75.8 ± 2.301 | 71.75 ± 2.052 | 5.4% ↓ | 202.0 ± 4.03 | 204.5 ± 5.06 | 1.23% ↑ |
| Group 2 | Chloroform extract | 278.4 ± 15.29 | 220.0 ± 16.3 | 22.5% ↓ | 133.2 ± 2.1 | 107.6 ± 4.32 | 19.55% ↓ |
| Group 3 | Methanolic extract | 408.6 ± 18.6 | 240.0 ± 19.8 | 41.2% ↓* | 143.5 ± 1.93 | 103.3 ± 3.12 | 27.72% ↓ |
| Group 4 | Aqueous extract | 342.0 ± 26.4 | 126.0 ± 31.2 | 63.26% ↓** | 155.2 ± 1.27 | 108.9 ± 1.09 | 29.84% ↓ |
| Group 5 | Glibenclamide | 336.7 ± 16.8 | 91.0 ± 26.8 | 72.9% ↓** | 135.2 ± 4.06 | 115.1 ± 3.9 | 14.7% ↓ |
| Group 6 | Diabetic control | 429.5 ± 15.67 | 330.5 ± 18.91 | 27.5% ↓ | 160.5 ± 3.08 | 116.5 ± 3.4 | 27.42% ↓ |

Values are Mean ± S.E; n = 5, Statistics: ONE-Way- ANOVA followed by Dunnet's test.
**p < 0.01, *p < 0.05, NS; Not significant Compared all readings to Diabetic Control

**Table 5:** Effect on serum lipid profiles of the treated rats

| Groups | Treatment | Serum lipid profiles | | | | |
|---|---|---|---|---|---|---|
| | | TG | TC | LDL | HDL | VLDL |
| Group 1 | Vehicle, 5% Tween 80 | 66.75 ± 4.40 | 62.25 ± 6.129 | 34.9 ± 5.29 | 11.5 ± 1.19 | 13.35 ± 0.88 |
| Group 2 | Chloroform extract | 55.5 ± 1.32* | 27.75 ± 1.109* | 11.08 ± 0.61* | 5.25 ± 0.322* | 11.05 ± 0.17 |
| Group 3 | Methanolic extract | 50.75 ± 0.85** | 54.25 ± 0.85* | 35.28 ± 0.53** | 10.25 ± 0.26* | 14.38 ± 0.25 |
| Group 4 | Aqueous extract | 58.75 ± 5.2 | 54.25 ± 5.34* | 36.23 ± 3.82** | 10.4 ± 1.02* | 15.5 ± 0.65* |
| Group 5 | Glibenclamide | 73.0 ± 1.29* | 51.5 ± 14.5* | 27.1 ± 11.86* | 9.8 ± 2.89* | 12.6 ± 0.25 |
| Group 6 | Diabetic control | 61.2 ± 1.49 | 34.25 ± 4.95 | 15.58 ± 3.74 | 6.32 ± 0.91 | 12.25 ± 0.29 |

Values are Mean ± S.E; n=5, Statistics: ONE-Way- ANOVA followed by Dunnet's test.
***p<0.0001, **p<0.01, *p<0.05.Compared all readings to Diabetic control

significant increase in triglycerides levels. Further in contrast to the diabetic control group a significant increase in concentrations of High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL) and Very Low Density Lipoproteins (VLDL) of methanolic extract treated groups and aqueous extract treated groups were observed but they are on par with healthy rats keeping the lipid profile of animals near to the normal values.

A significant increase in total Cholesterol of animals treated with methanolic extract, aqueous extract and Glibenclamide treated groups were observed, which were comparable to control group. Aqueous and Methanolic

extract treated groups show significant increase in HDL. LDL and VLDL levels in animals treated with aqueous extract, methanolic extracts of *Mangifera indica* are restored when compared to diabetic control animals.

## 6. Conclusion

Diabetes mellitus (type 1) of long duration is associated with several complications such as atherosclerosis, myocardial infarction, neuropathy, nephropathy, etc. These complications have long been assumed to be related to chronically elevated blood glucose levels. Disturbances in the uptake of glucose as well as glucose metabolism cause Diabetes mellitus. STZ-induced hyperglycaemia has been described as a useful experimental model to screen hypoglycaemic agents [11]. It is known that treatment of rats with high-dose STZ is an established model for type 1 diabetes, high-dose of STZ severely impairs insulin secretion leading to hyperglycaemia in rats. Besides hyperglycaemia, STZ-induced diabetic rats also shows an important lipolytic activity, due to the insulinopenic state which contributes to maintain the abnormally elevated plasma triglycerides and cholesterol levels [12]. The purpose of the present study was to assess the effects of the extracts of *mangifera indica* therapy on normal and STZ-induced diabetic rats.

Treatment (Acute) with Methanolic extract (200 mg/kg) in STZ-induced diabetic rats significantly reduced BGL when compared to diabetic control. While aqueous extract was less significant than the methanolic extract, Petroleum ether extract and chloroform extract were not significant in decreasing the blood glucose level.

High levels of total cholesterol and more importantly LDL cholesterol in the blood are major coronary risk factors [13]. The abnormally high concentration of serum lipids in the diabetic condition is due to mainly the increase in the mobilization of free fatty acids from the peripheral fat depots. Insulin deficiency or insulin resistance may be responsible for dyslipidemia. Oral administration of *Mangifera indica seed kernel* extracts lowered total cholesterol and triglycerides level in diabetic rats when compared to diabetic controls.

It is concluded that the long term (21 days) administration of methanolic and aqueous extract of *Mangifera indica* was effective in decreasing the blood glucose level and normalizing the other biochemical parameters in diabetic rats. The single dose study of the extract has no hypoglycemic effect on normal rats. Further studies need to be carried out to define the active principle(s) present in the extracts.

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