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Hypolipidemic and Hypoglycemic Effects of *Phyllanthus Maderaspatensis* L. Leaves in Streptozotocin-Induced Diabetic Rats

A.Rajeswari* And M. Shabana Begum

Department of Biochemistry, Muthayammal College of Arts and Science, Rasipuram Taluk, Namakkal District, Tamilnadu, India.

*Corresponding Author Email ID: bioraji21@gmail.com

Mobile Number: +91 9865999383

Abstract

The present analysis was aimed towards the assessing the hypolipidemic and hypoglycemic potentials in the leaves ethanolic extracts from *Phyllanthus maderaspatensis* L. leaves in streptozotocin (STZ)induced diabetes rats. Animals had been orally treated for sixty days with *P. maderaspatensis* extracts at dosages of 100, 200 and 300 mg/kg bw. The anti-diabetic impact was evaluated by determining blood glucose (BG) at 0, 15, 30, 45 and 60 days after STZ treatment method and, total cholesterol, triglycerides (TG) high density lipoprotein cholesterol (HDL-C), and lower density lipoprotein cholesterol (LDL-C) levels at sacrifice (day 61). Glibenclamide (0.6 mg/kg bw) was applied for comparing. STZ-provoked diabetic wistar rats proved modest to significant raises from the ranges of BG, TG, TC, LDL-C while body weight, HDL-C levels and relative weight of liver and pancreas were lowered in evaluation with normal rats. Administration in the leaves ethanolic extracts from *P.maderaspatensis* to STZ diabetic rats contributed to a noteworthy decrease in BG, TG, TC and LDL-C and the dosage 300 mg/kg bw of the leaves ethanolic extracts from *P.maderaspatensis* was the most effectual the HDL-C level was markedly greater after 60 days when assessed with untreated diabetic rats. A dosage-based raise in relative weight of diabetogenic organs was seen within the *P. maderaspatensis*groups. It can be also noticed that the leaves ethanolic extracts from *P.maderaspatensis*, particularly the dosage 300 mg/kg bw ($p<0.05$), generated a lot more effects than glibenclamide. Rats cured with glibenclamide (0.6 mg/kg bw) generally presented reduce effects in association with groups cured with the leaves ethanolic extracts from *P.maderaspatensis*. Outcomes of the current

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investigation showed that *P. maderaspatensis* extracts and particularly its ethanolic extract have antidiabetogenic potentials and advantageous outcomes on diabetic hyperlipidemia. Every one of these consequences might be because of the active biomolecules exposed from the *P. maderaspatensis* extracts like flavanoids and phenols and that could justify its ethnomedical use.

Keywords: *Phyllanthus maderaspatensis* L, hypoglycaemic activity, antihyperglycaemic activity, Biochemical Parameters.

INTRODUCTION

Diabetes is produced on by the breakdown of β-cells to make up for insulin endurance (Tangvarasittichai, 2015). This be in the leads to hyperglycaemia, which can in turn use harmful effects on β- cells. Proof for the significance of herb extracts inside the treatments for diabetes is developing (Gray, *et al*., 2017). Herbal plants are usually regarded as much less deadly and clear of side effects than synthetic types (Niggemann and Grüber, 2003).At present, the accessible prescription drugs employed for reduction in blood cholesterol levels are related with uncomfortable harmful effects. Medicinal plants happen to be commonly used for many generations as remedies for human diseases since they have ingredients of restorative value (Helkar, *et al*., 2016). Therefore, there is an increasing attention in explore on hypocholesterolemic secondary metabolites from medicinal plant. The herb belongs to family Euphorbiaceae can be a taxonomically complex and consists of different medicinal activities including hepatoprotective activity, lipid reducing activity, anti-diabetes activity and other actions (Zahidin, *et al*., 2017). The plants in the genus Phyllanthus of family members Euphorbiaceae (recently Phyllanthaceae) have higher status in traditional treatment in India, Brazil, China and also the Southeast Asian countries (Sarin, *et al*., 2014). Plants of this genus used in therapies since numerous of species has medicinally significant bioactive substances (Coe, and Anderson, 1996). It is noted that Phyllanthus species for instance *P. emblica, P. reticulates, P. debilis* and *P. maderaspatensis* are disseminated in various environmental zones of Sri Lanka.In English *P. maderaspatensis*. is normally termed as “Madras leaf flower”. It is a native herbaceous plant in India, Sri Lanka and Africa (Dissanayaka,*et al*., 2019).

Reports have exhibited that *P. maderaspatensis* have anti-bacterial, anti-microbial, anti-

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cataleptic and also other medicinal potentials for example deobstruent, stomachic, astringent, febrifugal, diuretic and antiseptic (Dissanayaka,*et al*., 2019). Also the results in of *P. maderaspatensis*. have expectorant and diaphoretic properties beneficial in strangury and sweats (Asha, *et al*., 2004).In India, *P. maderaspatensis* is traditionally exercised as an effectual hepato-protective professional inside the native medicine (Ayurveda) in addition to the powder from dried herb substance admixed with milk is commonly used to cure jaundice (Srirama, *et al*., 2010; Del Prete, *et al*., 2012).

Although dried plant material of *P. maderaspatensis*. is commonly used for biliary illnesses in Sri Lankan folk medicine, the herb is slightest concern because of its other medical benefit which includes hyphocholestrolemic activity (Rajasekaran, *et al*., 2013).Though *P. reticulates* and *P. emblica* reported to possess the anti-hypercholesterolemic activity, there was virtually no clinical research studies can be discoverd on the anti-hypercholesterolemic activity such as dose dependency of *P. maderaspatensis* (Kaur, *et al*., 2017). Furthermore, there was a need of studies in reliance of ethanolic extract of leaves of *P. maderaspatensis*(*Pm*L-Et) in anti-hypercholesterolemic activity. The present study may be the first analysis about the *Pm*L-Et on the food produced by hypercholectrolemic rats. For this reason, the research was directed to measure the hypocholesterolemic properties of crude *Pm*L-Et with dose dependent response on experimental animals.

MATERIALS AND METHODS

Collection and preparation of plant material

Fresh whole *P. maderaspatensis* collected from Salem Region, Tamil Nadu, India. The plant was authenticated by Dr. A. Balasubramanian, ABS Herbal Gardens in Salem, Tamil Nadu, India.

Drugs and chemicals

Glibenclamide was bought from Strides Arcolab Ltd. Bangalore, India and Streptozotocin was obtained from Himedia, Bangalore, India. All other chemicals used were of analytical grade.

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Animals

Male Wister rats of body weight 150-180g were obtained and maintained in the Department of Biochemistry, Muthayammal College of Arts and Science, Rasipuram, India. They were nourished on standard pellet diet (Amrut, Pune, India) and water *adlibitum*. The procedure of this study was sanctioned by Institutional ethical committee of Muthayammal College of Arts and Science (1416/PO/a/11/CPCSEA&7 MARCH 2011)

Preparation of the ethanol extracts

Plants were cleaned with fresh water, shade dried at room temperature and powdered. The powder was soxhlet extracted with ethanol (10 g/400 ml). The extraction was continual until a drop of solvent from the soxhlet siphon tube did not leave any residue when evaporated on a clean glass plate. Solvent was withdrawn from the extract under decreased pressure, using a rotary evaporator (VV2000, Heidolph, and Schwabach, Germany). Extract was stored in -20^{o}C freezer until use.

Preliminary phytochemical screening

Qualitative phytochemical evaluation was executed on *Pm*L-Etto divulged the presence or not of flavonoids, sterols, phenols, alkaloids, saponins all these experiments were executed (Brindha and Sasikala, 1981).

Study of *Pm*L-Et in experimental rats

Adult (150-180 g) male Wister albino rats have been created diabetes having an intraperitoneal injection of STZ, (45 mg/kg bw) dissolved in citrate buffer (0.1 M, pH 4.5). STZ injected animals demonstrated massive glycosuria and hyperglycaemia within a few days. Diabetes was confirmed in STZ provoked rats by determining the fasting blood sugar levels concentration, 72 h after injection with STZ. Albino rats with BG level above 250 mg/dL were actually regarded as being diabetic person and were utilized in the experiment.

Group I offered like a normal control and received appropriate volumes of vehicle (distilled water) orally. Group II – VI were created diabetic intravenously, by an intravenous injection for

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any freshly prepared STZ solution in the dosage of 45mg/kg bw in acidified saline solution (0.9%; pH 4.5). In this instance, the group II animals obtained simply the acidified saline solution. Following 72h, when the condition of DM was stabilized, the animals with BG levels above 200mg/dl ended up being determined towards the study. Group III and V received the *Pm*L-Et by oral about the doses of: 100, 200 and 300mg/kg. Animals of group VI had gotten glibenclamide in the dose of 600µg/kg as a standard. Blood samples examples for BG estimated through the suggestion of tail of rats before administration of drugs. All test substances have been administered by gastric gavage for 60 days.

Biochemical parameters

Glycaemia was measured at 0, 15, 30, 45 and 60 days after pharmacological treatments (Folin, and Wu, 1919). Body weight and comparable weights of pancreas and liver had been captured. All of the six groups of rats were sacrificed one day after the last treatment (day time 61) by cervical dislocation. Blood was collected to the estimations of total cholesterol (TC) (Parekhand Jung, 1970), HDL cholesterol (HDL-C), LDL-cholesterol (LDL-C) (Friedewald, *et al*., 1972), and triglycerides (TG) (Foster, and Dunn, 1973).

Statistical Analysis

All data are expressed as mean ± S.E.M. One-way analysis of variance (ANOVA) was performed followed by Tukey's test to compare the differences between treatments. Differences were considered statistically significant for $p < 0.05$.

RESULTS

Phytochemical analysis

Qualitative phytochemical screening of the *Pm*L-Etshowed Flavonoids, Phenol, Alkaloids and Saponins (Table 1).

Table 1 Results of the phytochemical screening of *P. maderaspatensis* extracts

Group of Compounds	**Ethanol Extract**
Flavonoids	+

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Sterols	-
Phenol	+
Alkaloids	+
Saponins	+

+ - Present and - - Absent

Effects of *P. maderaspatensis* on body weight and relative organ weights

Introduction of diabetes (untreated diabetes rats) significantly ($p<0.05$) diminished the body weight in evaluation with controls. Oral therapy of diabetes animals with glibenclamide (600 µg/kg bw) or *Pm*L-Et significantly ($p<0.05$) improved the body weight through the whole time of study period. (Table 2). The relative weight loads of pancreas and liver were also reduced in all diabetic rats in comparison to controls. However, with consider to diabetes animals, a dose dependent raised in the relative weights of such important organs was witnessed inthe *P. maderaspatensis* groups. It could be also realized that the *Pm*L-Et, particularly the serving 300 mg/kg bw, created much more results ($p<0.05$) than glibenclamide and *Pm*L-Et (Table 2).

Table 2: Effects of *P. maderaspatensis* on body weight, relative weights of liver and pancreas and, lipid profile on STZ-induced diabetic rats

Groups	Body weight(g)		Relative organ weight (mg/g)		Lipid profile(mg/dl)				
	Initial	Final	Liver	Pancreas	TC	VLDL-C	LDL-C	HDL-C	TG
Control	153.83±1.42	197.83±2.74	23.00±0.86	6.2±0.15	130.52±0.42	23.48±0.12	47.83±0.99	59.22±0.61	117.38±0.6
STZ induced	155.00±1.32	114.5*±3.32	11.83±0.31*	2.13±0.18*	249.85±0.82*	35.6±0.76*	176.2±1.27*	38.05±0.52*	178±3.79*

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STZ induced+100 mg/kg bw of *Pm*L-Et	155.50±1.15	165.33±2.29	14.67±0.33	3.43±0.13	208.68±1.54	33.04±0.28	131.86±1.33	43.78±0.52	165.2±1.39
STZ induced+200 mg/kg bw of *Pm*L-Et	153.33±0.49	184.67±5.06	16.50±0.43	4.48±0.11	189.35±0.56	29.34±0.11	111.66±0.69	48.35±0.19	146.72±0.54
STZ induced+300 mg/kg bw of *Pm*L-Et	154.83±1.76	190.17±1.83	20.00±0.77	5.43±0.16	169.35±0.76	26.6±0.15	90.56±0.96	52.2±0.23	133±0.76
STZ induced+600 µg/kg bw of Glibenclamide	154.00±0.86**	193.00±1.15**	21.5±0.43**	6.01±0.17**	141.35±0.89**	24.57±0.1**	60.56±0.98**	56.22±0.28**	122.83±0.49**

The values are means ± SEM; number of animals per group = 6.

*: p<0.05: significantly different compared to contrgroupsol groups.

**p <0.05 significantly different compared to STZ induced diabetic.

Effects of *P. made* Values ***raspatensis*** **on blood glucose**

Table 3 shows the impact of *Pm*L-Et on BG levels of Wistar rats after sixty days of constant treatment. Sequential injections of STZ induced a significant boost (p<0.05) in BG levels in all of the sets of rats in contrast to their respective standard BG levels (at the time of group) and also to control values. At all-time points, BG levels remained unchanged (p<0.05) in normal rats treated with distilled water. Even so, oral administration of plant extracts in addition to glibenclamide to diabetic rats provoked a dose-dependent reduce (p<0.05) in BG concentrations. Thus after sixty days of constant treatment method, the amount 300 mg/kg bw of the *Pm*L-Et generated probably the most relieving outcomes when compared with glibenclamide.

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Effects of *P. maderaspatensis* on lipid profile

The diabetic problem in rats (untreated diabetics) increased TC, LDL-C and TG levels and minimized HDL-C level ($p<0.05$) in comparison to control rats (non diabetic rats). Treatment for STZ-induced diabetic rats with *P. maderaspatensis* extracts and especially the *Pm*L-Et generated opposite results verified with a lessen ($p<0.05$) in serum TC and LDL-C and an increase in the HDL-C concentration when compared to untreated diabetes. A propensity to a decline in TG intensities had also been noted with regards to diabetic rats getting distilled drinking water. In general, glibenclamide created very similar consequences. As above observed, the *Pm*L-Etperformed to be more effective and stronger at great dose (300 mg/kg) than glibenclamide (Table 3)

Table 3: Effects of *P. maderaspatensis*on blood glucose in STZ-induced diabetic rats

Groups	Fasting blood glucose level (mg/dl)				
	0^{th} day	15^{th} day	30^{th} day	45^{th} day	60^{th} day
Control	97.50±0.76	98.83±2.4	100.50±2.43	96.50±1.09	96.00±2.16
STZ induced	98.00±1.15	131.83±2.41	155.50±1.78	170.67±1.15	184.17±3.09
STZ induced+100 mg/kg bw of *Pm*L-Et	94.67±1.09	124.00±1.44	129.83±3.21	131.00±4.11	135.50±2.93
STZ induced+200 mg/kg bw of *Pm*L-Et	96.50±1.48	117.17±2.07	122.00±2.63	124.33±0.84	126.17±0.6
STZ induced+300 mg/kg bw of *Pm*L-Et	97.33±0.8	105.33±3.22	100.17±1.9	101.33±3.6	99.83±2.2
STZ induced+600 µg/kg bw of Glibenclamide	95.33±0.88	103.50±2.22	100.83±2.26	98.83±1.38	97.50±1.93

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The values are means ± SEM; number of animals per group = 6.

*: $p<0.05$: significantly different compared to control groups.

**$p<0.05$ significantly different compared to STZ induced diabetic groups

Discussion

STZ inhibits DNA functionality in mammalian and microbial tissues. In microbe tissues, it renders particular effect with cytosine groups, causing damage and repair to DNA. The biochemical mechanism results in mammalian cell death (Goyal, *et al*., 2016). STZ helps prevent cellular reproduction having a much smaller dosage compared to dose required for suppressing the substrate connection to the DNA or suppressing of the enzymes associated with DNA synthesis (Wang, *et al*., 2019). Even though STZ prevents admittance of tissues into mitosis but no special period of cellular cycle is particularly sensitive to its mortal consequences. STZ, which is used in intravenously form by speedy injection or frequent simple diffusion, stimulates the cells (Macrae, 2011). Metabolically, a small deviation of the BG showing pain from the regular limit has been seen in patients cured with a precise amount of STZ, which is generally reversible. However, the insulin shock, which is one of its other outcomes, is irrevocable (Dissassa, *et al*., 2013).

In diabetic rats cured with *Pm*L-Et, a remarkable decrease ($p<0.05$) in BG levels was noted when compared to particular standard principles (Day 0). These effects additional keep the hypoglycemic activity of *P.maderaspatensis* previously stated in BG overloaded normal control rats. It can be generally thought that most of the herbals with antidiabetic possibilities have been obtained to include a diversity of elements accountable for the stated activities (Khan, *et al*., 2012). Therefore, phytochemical tests uncovered the presence of Flavonoids, Phenol, Alkaloids and Saponinsin *Pm*L-Et. This has been established that flavanoids and phenols encouraged insulin secretion through their antioxidant properties (Maier, *et al*., 2009). Oxidative stress has been exposed to play a key part from the connection of diabetes (Asmat, *et al*., 2016). STZ generates O_2 radicals in body, which result in pancreatic trauma and might be accountable for elevated BG and also lipid peroxidation (Nain, *et al*., 2012). Consequently, antioxidants may have a part in the reduction of diabetes. From the effects acquired in this particular work, it could

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be recommended that *P. maderaspatensis* may improve the antioxidant shield against ROS made under hyperglycemic situation which could protect β-cells against decrease, and reveal the antidiabetic activity. The *in vitro* antioxidant potentials of *P. maderaspatensis* previously claimed by utilizing extracts from stem bark, leaves, root sand wood of this medicinal plant could be of great importance from the knowledge of this proposed *in vivo* antioxidant property of *P. maderaspatensis*. It is a well-established proven fact that numerous medicinal plants possess antioxidant potentials which might be valuable under diabetes conditions (Trujillo, *et al*., 2013). Results from this study also suggest that the *Pm*L-Et, particularly the dose 300 mg/kg bw, produced more relieving effects. This inspections strengthens the detail that *Pm*L-Et are typically identified for their higher substances in chemical compounds competent at generating biological activities (Swamy, *et al*., 2015).With regards to the lowering BG concentrations, it can be suggested that *P. maderaspatensis* may act by revitalizing insulin secretion likewise to glibenclamide, activating intensifying restoration of the injured β-cells after consecutive injection of STZ or potentiating BG uptake and employ by a variety of tissue(Dixit, *et al*., 2014). The enhancements experiential in the body weight and in the comparable weight of the pancreas and liver organ of diabetes animals after herb extract treatment (Ezejiofor, *et al*., 2013)further help these recommended pancreatic and extra-pancreatic elements of activity of *P. Maderaspatensis* (Munshi, *et al*., 1993).

As anticipated, untreated diabetic animals revealed a substantial increase in serum TC, TG and LDL-C concentrations against low levels of HDL-C (Pierre, *et al*., 2012). This raise in serum lipids is majorly as a result of greater fatty acid deployment from adipose tissue (Wagenmakers, *et al*., 2006). Then insulin has a repressive action on HMG-CoA reductase, the real vital enzyme in cholesterol biosynthesis, insulin deficit or insulin level of defiance may therefore be accountable for hyperlipidemia (Pierre, *et al*., 2012). Treatment for diabetic rats with *P. maderaspatensis* extracts, specially its *Pm*L-Et (300 mg/kg), inverted although not entirely dyslipidemia as evinced with the significant reduce ($p<0.05$) in TC, LDLC and TG coupled to the intensification in HDL-C ($p<0.05$). These alleviating outcomes clearly denote the antihyperlipidemic prospective of *P. maderaspatensis*, and might also accounts inside the improvement of liver weight as above noted. It is also recommended that the antihyperlipidemic results of *P. maderaspatensis*permit through a reduction in digestive tract cholesterol absorption

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or even a reduction in the biosynthesis of cholesterol explicitly by lowering the action of HMG-CoA reductase inhibitors.

CONCLUSION

Commencing with this study, we can conclusively declare that, *Phyllanthus maderaspatensis* L. extract and specifically the ethanolic extract hold antidiabetogenic potentials and helpful consequences on diabetic hyperlipidemia. All of these beneficial consequences about this rat could possibly be due to the bioactive factors uncovered from the *Phyllanthus maderaspatensis* L. extracts including flavonoids and phenols.

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