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Antidiabetic and antihyperlipidaemic activity of ethanol extract of *Melastoma malabathricum* Linn. leaf in alloxan induced diabetic rats

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PEER REVIEW

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Comments

This a good study in which the authors validated that, *M. malabathricum* leaf is a potential antidiabetic drug that may be used for maintaining traditional use.
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ABSTRACT

Objective: To evaluate the antidiabetic and antihyperlipidaemic effect of ethanol extract of *Melastoma malabathricum* (*M. malabathricum*) Linn. leaf in alloxan induced diabetic rats.

Methods: Diabetes was induced in albino rats by administration of alloxan monohydrate (150 mg/kg *i.p*). the ethanol extracts of *M. malabathricum* at a dose of 150 and 300 mg/kg of body weight were administrated at a single dose per day to diabetes induced rats for a period of 14 d. The effect of ethanol extract of *M. malabathricum* leaf extract on blood glucose, plasma insulin, creatinine, glycosylated haemoglobin, urea serum lipid profile [total cholesterol, triglycerides, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol, high density lipoprotein-cholesterol and phospholipid, serum protein, albumin, globulin, serum enzymes (serum glutamate pyruvate transaminases), serum glutamate oxaloacetate transaminases, and alkaline phosphatase] were measured in the diabetic rats.

Results: In the acute toxicity study, ethanol extract of *M. malabathricum* leaf was non-toxic at 2 000 mg/kg in rats. The increased body weight, decreased blood glucose, glycosylated haemoglobin and other biochemical parameters level were observed in diabetic rats treated with both doses of ethanol extract of *M. malabathricum* leaf compared to diabetic control rats. In diabetic rats, ethanol extract of *M. malabathricum* leaf administration, altered lipid profiles were reversed to near normal than diabetic control rats.

Conclusions: Ethanol extract of *M. malabathricum* leaf possesses significant antidiabetic and antihyperlipidaemic activity in diabetic rats.

KEYWORDS

Melastoma malabathricum, Antidiabetic, Antihyperlipidaemic, Alloxan, Glibenclamide, SGOT, SGPT, HbA1c

1. Introduction

Diabetes mellitus is an epidemic occurring in adults throughout the world and is the leading cause of kidney failure, heart attack, blindness and lower limb amputation. It is the fourth main cause of death in most developed countries. The prevalence of diabetes is estimated to reach 330 million by the year 2025, according to International Diabetes Federation, with the greatest potential increase being in Africa and Asia. This numerical increase will occur in developing countries. By the year 2025, over 75% of people with diabetes will reside in developing countries, as compared to 62% in 1995[1].

Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides and glinides. Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycemic agents is one

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of the important areas of investigations[2]. Many herbs and plants have been described as possessing hypoglycemic activity when taken orally[3]. According to the World Health Organization, there are more than 1 200 plant species worldwide used in the treatment of diabetes mellitus and substantial number of plant showed effective hypoglycemic activity after laboratory testing[4].

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically in antidiabetic and antihyperlipidemic remedies. Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibiting the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of the plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids *etc.* that are frequently implicated as having antidiabetic effect[5]. However, the study of plant for hypoglycemic, antioxidant and hypolipidemic activities may give new pharmacological approaches in the treatment of diabetes mellitus[6].

Melastoma malabathricum (*M. malabathricum*) Linn. belongs to the Melastomataceae family. It is also called the Singapore Rhododendron or Sendudok. It is an erect shrub or small tree with the height of 1.5 to 5 m. It was traditionally used to treat diarrhoea, dysentery, leucorrhoea, hemorrhoids, wounds, infection during confinement, toothache, flatulence, sore legs, and thrush and it is also used by the Jah hut people in Malaysia to cure diarrhea[7]. There is no report on the antidiabetic and antihyperlipidaemic potential of this plant extract so far. The main objective of this study was to assess the antidiabetic and antihyperlipidaemic effect of ethanol extracts of leaf of *M. malabathricum* in alloxan induced diabetic rats.

2. Materials and methods

2.1. Plant material

The leaves of *M. malabathricum* were freshly collected from Daudeli, Joide Taluk, Hubli district, North Karnataka. With the help of local flora, a voucher specimen was retained in Ethnopharmacology Unit, Research Department of Botany, V. O. Chidambaram College, Tuticorin for further reference.

2.2. Preparation of plant extract for phytochemical screening and antidiabetic studies

The *M. malabathricum* leaf was shade dried at room temperature and the dried leaf was powdered in a Wiley mill. Hundred grams of powdered leaf was packed in a Soxhlet apparatus and extracted with ethanol. The extracts were subjected to qualitative test for the identification of various phytochemical constituents as per the standard procedures[8,9]. The ethanol extracts were concentrated in a rotary evaporator. The concentrated ethanol extracts were used for antidiabetic studies.

2.3. Animals

Normal healthy male Wistar albino rats (180-240 g) were housed under standard environmental conditions at temperature (25±2) °C and light and dark (12:12 h). Rats were fed with standard pellet diet (Goldmohur brand, MS Hindustan lever Ltd., Mumbai, India) and water *ad libitum*. Study was carried out as per IAFC approval No: 82/PHARMA/SCRI, 2010.

2.4. Acute toxicity study

Acute oral toxicity study was performed as per Organization for Economic Co-operation and Development-423 guidelines (acute toxic class method), albino rats (n=6) of either sex selected by random sampling were used for acute toxicity study[10]. The animals were kept fasting for overnight and provided only with water, after which the extracts were administered orally at 5 mg/kg body weight by gastric intubations and observed for 14 d. If mortality was observed in two out of three animals, then the dose administered was assigned as toxic dose. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for higher doses such as 50, 100, and 2000 mg/kg body weight.

2.5. Induction of diabetes in experimental animal

Rats were induced diabetes by the administration of simple intraperitoneal dose of alloxan monohydrate (150 mg/kg)[11]. After 2 d of alloxan injection, rats screened for diabetes having glycosuria and hypoglycemia with blood glucose level of 200-260 mg/100 mL were taken for the study. All animals were allowed free access to water and pellet diet and maintained at room temperature in plastic cages.

2.6. Experimental design

In the present investigation, a total of 30 rats (24 diabetic surviving rats and six normal rats) were taken and divided into five groups of six rats each. Group I: normal untreated rats; Group II: diabetic control rats; Group III: diabetic rats given ethanol extract of *M. malabathricum* leaf (150 mg/kg body weight); Group IV: diabetic rats given ethanol extract of *M. malabathricum* leaf (300 mg/kg body weight); Group V: diabetic rats given standard drug glibenclamide (600 μg/kg body weight).

The animals were sacrificed at the end of experimental

period of 14 d by decapitation. Blood was collected, sera separated by centrifugation at 3 000 *g* for 10 min.

2.6.1. Estimation of insulin, glucose, urea, creatinine and glycosylated haemoglobin

Serum glucose was measured by the o-toluidine method[12]. Insulin level was assayed by ELISA kit[13]. Urea estimation was carried out by the method of Varley[14]; serum creatinine was estimated by the method of Owen *et al*[15]. Glycosylated haemoglobin (HbA1c) estimation was carried out by a modified colorimetric method of Karunanayake and Chandrasekharan[16].

2.6.2. Estimation of protein, albumin, globulin, SGPT, SGOT, ALP

Serum protein[17] and serum albumins were determined by quantitative colorimetrically method by using bromocresol green. The total protein minus the albumin gives the globulin, serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) was measured spectrophotometrically by utilizing the method of Reitman and Frankel[18]. Serum alkaline phosphatase (ALP) was measured by the method of King and Armstrong[19].

2.6.3. Estimation of lipids and lipoprotein

Serum total cholesterol (TC)[20], total triglycerides (TG)[21], low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL- C)[22], high density lipoprotein cholesterol (HDL-C)[23] and phospholipids[24] were analyzed.

2.7. Statistical analysis

The data were analyzed using Student's *t*-test statistical methods. For the statistical tests, *P* values less than 0.01 and 0.05 were taken as significant.

3. Result

3.1. Phytochemical constituents

The phytochemical screening of ethanol extract of *M. malabathricum* leaf revealed the presence of alkaloid, catechin, coumarin, flavonoid, phenol, saponin, steroid, tannin, terpenoid, sugar, glycoside and xanthoprotein.

3.2. Acute toxicity test

The extract was safe up to a dose of 2 000 mg/kg body weight. Behavior of the animals was closely observed for the first 8 h then at an interval of every 4 h during the next 48 h, the extract did not cause mortality on rats during 48 h observation or any behavioral change.

3.3. Body weight and fasting blood glucose

In the present study, alloxan induced diabetic rats showed significant ($P<0.01$) reduction in body weight. Administration of ethanol extract of *M. malabathricum* leaf (150 and 300 mg/kg) and glibenclamide (600 mg/kg) significantly ($P<0.05$) increased the body weight within 14 d (Table 1). Fasting blood glucose levels of the diabetic control rats were higher than those of normal rats. A significant ($P<0.05$) dose dependent decrease in blood glucose levels was observed in the diabetic treated group from an initial level of 232.14 mg/dL to the level of 144.36 mg/dL and from 213.12 mg/dL to 124.33 mg/dL after the treatment at a dose of 150 mg/kg and 300 mg/kg respectively for 14 d (Table 1).

3.4. Blood glucose level and other parameters

Table 2 shows the levels of blood glucose, serum insulin, urea, creatinine and glycosylated hemoglobin of normal, diabetic control and drug treated rats. There was a significant ($P<0.01$) increase blood glucose level in alloxan induced diabetic rats (Group II) when compared with normal rats (Group I). Administration of leaf extract of *M. malabathricum* (Groups III & IV) and glibenclamide (Group V) tended to bring the parameters significantly ($P<0.05$, $P<0.01$) towards the normal. Serum insulin level of diabetic control group was significantly ($P<0.01$) decreased when compared to normal control group (Group I). The extract and glibenclamide group of diabetic rats significantly ($P<0.01$) increased the serum insulin. A significant ($P<0.05$) elevation in urea and creatinine was observed in alloxan induced diabetic rats (Group II) when compared to control rats. The *M. malabathricum* extracts were administrated orally to diabetic rats for 14 d reversed the urea and creatinine level to near normal. Administration of ethanol extract of *M. malabathricum* leaf (300 mg/kg) and glibenclamide significantly ($P<0.05$) reduced HbA1c level compared to

Table 1
Effect of *M. malabathricum* leaf extract on the body weight and fasting blood glucose in normal, diabetic and diabetic treated rats.

Treatment groups	Mean initial body weight (g)	Mean final body weight (g)	Mean weight Gain (G ↑)/loss (L ↓) (g)	Fasting bloodglucose (mg/dL)	
				Initial	Final (after 14 d)
Group I	189.54±5.11	197.65±6.36	8.12 ↑	69.88±1.92	73.95±1.64
Group II	192.63±8.24	173.94±5.24	18.69 ↓ **	248.56±2.84	263.16±5.36
Group III	188.31±5.36	196.47±4.14	8.16 ↑ [a]	232.14±2.54	144.36±4.86[b]
Group IV	184.51±5.33	194.93±4.38	10.42 ↑ [a]	213.12±5.28	124.33±4.37[b]
Group V	196.58±9.34	216.42±7.39	19.84 ↑ [a]	229.66±6.16	104.53±4.35[b]

Values are expressed as mean±SEM, $n=5$. **: $P<0.05$ comparison with normal control *v.s.* diabetic and drug treated; [a]: $P<0.05$ diabetic control *v.s.* drug treated; [b]: $P<0.05$ comparison with initial *v.s.* final.

Table 2
Effect of *M. malabathricum* leaf extracts on the serum insulin, glucose, urea, creatinine and HbA1c level of normal, diabetic induced and drug treated rats.

Treatment groups	Insulin (mIU/mL)	Glucose (mg/dL)	Urea (mg/dL)	Creatinine (mg/dL)	HbA1c (%)
Group I	21.830±1.130	73.81±3.54	12.05±1.04	0.73±0.12	4.61±0.52
Group II	9.190±0.948**	198.39±2.61**	29.63±1.85*	2.45±0.35*	9.89±0.25**
Group III	14.300±1.670a	134.66±1.56a	21.54±1.26	1.86±0.48	7.26±0.76ns
Group IV	18.510±1.250c	114.51±1.84c	14.45±1.38	1.29±0.15	5.16±0.81a
Group V	19.730±1.090c	109.38±1.84c	13.05±1.56a	1.05±0.11a	5.21±0.62a

Values are expressed as mean±SEM, n=5. *: comparison made between normal control to diabetic control and drug treated groups; *: P<0.05, **: P<0.01; a: comparison made between diabetic control to drug treated groups; a: P<0.05, c: P<0.01; ns: not significant.

Table 3
Effect of *M. malabathricum* leaf extracts on the serum protein, albumin, globulin, SGPT, SGOT and ALP level of normal, diabetic induced, and drug treated rats.

Treatment groups	Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)	SGPT (μ/L)	SGOT (μ/L)	ALP (μ/L)
Group I	7.93±0.16	4.63±0.14	3.30±0.11	18.53±1.62	20.16±1.33	184.93±3.65
Group II	6.02±0.19*	3.84±0.21*	2.18±0.24	97.18±3.54*	89.25±1.91*	226.16±4.84*
Group III	6.96±0.15a	4.12±0.11	2.84±0.14	38.56±1.26	49.66±1.76	204.08±4.56a
Group IV	8.26±0.65a	4.86±0.53	3.40±0.52	27.59±1.84	30.51±1.94	191.56±2.89a
Group V	7.96±0.38ns	4.03±0.45	3.93±0.24	21.94±1.12	25.88±1.65	173.94±2.16a

Values are expressed as mean±SEM, n=5. *: comparison made between normal control to diabetic control and drug treated groups; *: P<0.05; a: comparison made between diabetic control to drug treated groups; a: P<0.05; ns: not significant.

Table 4
Effect of *M. malabathricum* leaf extracts on the serum lipid profile of normal, diabetic induced, and drug treated rats.

Treatment groups	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL-C (mg/dL)	V-LDL (mg/dL)	Phospholipid (mg/dL)
Group I	103.34±2.18	93.61±1.64	42.98±2.16	41.64±1.32	18.72±1.03	159.97±3.51
Group II	214.26±4.76**	198.16±4.27**	26.36±1.65**	148.27±3.68**	39.63±1.26*	258.69±5.33**
Group III	164.13±2.48c	156.31±1.74c	31.14±2.14a	96.64±1.34a	34.44±1.34a	224.36±2.36a
Group IV	141.65±2.27c	136.18±1.13c	36.39±2.31a	78.02±1.16c	27.24±1.48a	194.06±2.17a
Group V	119.57±1.21c	124.74±2.68c	23.54±1.88	71.08±1.21c	24.95±1.23a	174.41±1.92c

Values are expressed as mean±SEM, n=5. *: Comparison made between normal control to diabetic control and drug treated groups; *: P<0.05, **: P<0.01; a: comparison made between diabetic control to drug treated groups; a: P<0.05; c: P<0.01; ns: not significant.

diabetic control rats.

3.5. Biochemical parameters

The level of total protein, albumin, globulin and liver marker enzymes such as SGPT, SGOT and ALP in the serum of diabetic rats are presented in Table 3. Significant reductions in serum protein, albumin and globulin were observed in alloxan induced diabetic rats (Group II) when compared to control rats (Group I). On administration of ethanol extract of *M. malabathricum* leaf to the diabetic rats, protein albumin and globulin levels were found to be restored in normal. Also, the SGPT, SGOT and ALP levels were elevated significantly in alloxan induced diabetic rats compared to control rats. Both the doses of *M. malabathricum* leaf extracts and glibenclamide treatment significantly reduced above parameters compared to diabetic control rats.

3.6. Lipid profiles

Table 4 shows the levels of TC, TG, LDL-C, VLDL-C, HDL-C and phospholipid in the serum of diabetic rats showed significantly (P<0.01) increased serum lipid profiles except HDL-C when compared with normal rats. The ethanol extract of *M. malabathricum* leaf treated rats showed a significant (P<0.01, P<0.05) decrease in the content of lipid profiles when compared with diabetic induced rats. Similarly HDL-C level decreased in alloxan induced diabetic rats when compared with normal rats. Administration of ethanol extract of *M. malabathricum* leaf and glibenclamide to the diabetic rats. HDL-C level was found to be restored to normal.

4. Discussion

Diabetes mellitus is one of the most familiar chronic diseases associated with carbohydrate metabolism. It is also an indication of co-morbidities such as obesity, hypertension and hyperlipidemia which are metabolic complications of both clinical and experimental diabetes. Despite the fact that diabetes mellitus has high prevalence, morbidity, and mortality globally; it is regarded as a non curable but controllable disease. Different synthetic drugs, plant remedies and dietary modification play an efficient role in the reduction of the suffering that it causes. The potential role of medicinal plants as hypoglycemic agents has been reviewed by several researchers[25,26].

Pancreas is the primary organ involved in sensing

the organism's dietary and energetic states via glucose concentration in the blood and in response to elevated blood glucose, insulin is secreted.

Alloxan is one of the usual substances used for the induction of diabetes mellitus apart from streptozotocin. Alloxan has a destructive effect on the beta cells of the pancreas.

Alloxan causes a massive reduction in insulin release by the destruction of β-cells of the islets of langherhans, thereby inducing hyperglycemia. Insulin deficiency leads to various metabolic alterations in the animals *viz*. increased cholesterol, increased levels of alkaline phosphate and transaminases[27,28].

In diabetic condition, elevated blood glucose, reduction in body weight, polyuria, polydipsia and polyphagia are commonly observed. In the present study, induction of diabetes by alloxan produced increase in blood glucose level, decrease in body weight and polyuria. In diabetic rats, observed reduction in body weight was possible due to catabolism of fats and protein[29]. The administration of ethanol extract of *M. malabathricum* leaf improves body weight compared to diabetic control rats which indicates preventive effect of *M. malabathricum* on degradation of structural proteins. The increase in blood glucose level after alloxan administration may be due to insulin deficiency or resistance state in diabetic rats. Administration of ethanol extract of *M. malabathricum* leaf significantly reduced blood glucose level in diabetic rats which represents reversal of insulin resistance or increasing insulin secretion possibly by regeneration of damaged pancreatic β-cells in alloxan-induced diabetic rats[30]. Earlier, many plants have been studied for their hypoglycemic and insulin release stimulatory effects[31-36].

In diabetes, elevated levels of serum urea and creatinine are observed which may be due to renal damage caused by abnormal glucose regulation or elevated glucose and glycosylated protein tissue levels[37]. In present study, significant increase in serum urea and creatinine levels were observed in diabetic rats compared to normal control rats which indicate impaired renal function in diabetic rats. The treatment with ethanol extract of *M. malabathricum* lowered the above parameters significantly compared to diabetic control rats and it showed protective effect of ethanol extract of *M. malabathricum* on the kidneys.

In diabetes, HbA1c is considered as a diagnostic marker and helps to know about degree of protein glycation, long-term blood sugar level and correlation of diabetes associated complications[38,39]. HbA1c has been found to be increased over a long period of time in diabetes. During diabetes, the excess of glucose present in blood reacts with haemoglobin to form glycosylated haemoglobin[40]. The rate of glycation is proportional to the concentration of blood glucose. In present study, alloxan induced diabetic rats showed significant increase ($P<0.01$) HbA1c level compared with normal rats. The ethanol extract of *M. malabathricum* whole plant treated rats showed a significant decrease ($P<0.05$) in the content of glycosylated haemoglobin that could be due to an improvement in glycemic status.

In diabetic condition, occurrence of reduction in protein and albumin may be due to proteinuria, albuminuria or increased protein catabolism, which are clinical markers in diabetic nephropathy[41]. The protein and albumin level was reduced after the induction of diabetes and treatment of ethanol extract of *M. malabathricum* increased both levels considerably in diabetic rats towards normal level. This action possibly is through increase in the insulin mediated amino acid uptake, enhancement of protein synthesis and/or inhibition of protein degradation[42]. Also, increased serum SGOT, SGPT and ALP levels were reported in diabetes and it may be due to liver dysfunction[43]. In this study, increased level of SGOT, SGPT and ALP was observed in alloxan-induced diabetic rats which may have occurred by leakage of enzymes from the liver cytosol into the blood stream; it represents the toxicity of alloxan on liver. Diabetic rats treated with ethanol extract of *M. malabathricum* leaf significantly reduced both enzyme levels which represents the protective action of ethanol extract of *M. malabathricum* leaf in diabetic condition.

The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia[44]. The abnormal high concentrations of serum lipids in diabetic animals are mainly due to an increased mobilization of free fatty acids from peripheral fat depots[45]. In the present study, significantly increased levels of serum TC, TG, V-LDL and LDL as well as marked reduction in serum HDL level in diabetic rats. Administration of both the doses of ethanol extract of *M. malabathricum* leaf decreased levels of TC, LDL, V-LDL and TG levels as well as increased the level of HDL in diabetic rats. The above action could be beneficial in preventing diabetic complications such as coronary heart diseases and atherosclerosis in diabetic condition. Increased phospholipids levels in serum were reported by Anitha *et al*. in alloxan induced diabetic rats[46]. Administration of ethanol extract of *M. malabathricum* leaf glibenclamide decreased the levels of phospholipids.

In the present study, the administration of *M. malabathricum* leaf extracts to alloxan induced hyperglycemic rats demonstrated prominent reduction in blood sugar level, normalization of serum biochemical profile including lipid content, as compared to alloxan control rats. The phytochemical analysis has shown the presence of potent phytochemicals such as flavonoids, terpenoids, glycosides, steroids, saponin and phenols. Several authors reported that flavonoids, steroids/terpenoids, phenolic acids are known to be bioactive antidiabetic principles[47,46]. Flavonoids are known to regenerate the damaged beta cells in the alloxan induced diabetic rats and acts as insulin secretagogues[48]. In the present study, the phytochemical analysis of ethanol extract of *M. malabathricum* leaf clearly prints out the presence of above said active principles. The preliminary investigation on the antihyperglycemic, antihyperlipidaemic and antioxidant efficacy of ethanol extract of *M. malabathricum* leaf will be significant to proceed further in this path for the isolation of active principles responsible for the antidiabetic activity.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Diabetes mellitus is still not completely curable by current antidiabetic drugs. Insulin therapy is the only satisfactory approach in diabetes mellitus, even though it has several drawbacks such as insulin resistance, anorexia, brain atrophy and fatty liver in chronic treatment. Treatment of type 2 diabetes mellitus patients with sulfonylureas and biguanides is always associated with side effects. So, herbal drugs are gaining popularity in the treatment of diabetes mellitus. The major merits of herbal medicines seem to be their efficacy, low incidence of side effects, and low cost. The paper is on analytical report of *M. malabathricum* leaf ethanolic extract. Relevant established protocol were used to analyse the antidiabetic and antihyperlipidaemic activity of ethanolic extract of the plant.

Research frontiers

Many traditional plant treatments for diabetes are used through out the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic one. Based on the WHO recommendations, hypoglycemic agents of plant origin used in traditional medicine are important.

Related Reports

Similar work has been done earlier in other plants using the same methodology.

Innovations and breakthroughs

The present study indicates that ethanolic extract of *M. malabathricum* leaf decreased the blood glucose levels in diabetic rats and increased the insulin level.

Applications

The results of this study give scientific credibility to the use of the plant *M. malabathricum* leaf in the treatment of many diabetics.

Peer review

This a good study in which the authors validated that, *M. malabathricum* leaf is a potential antidiabetic drug that may be used for maintaining traditional use.

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