Review Article

A decade anti-diabetic potential of *murraya koenigii* (curry leaf): A narrative review

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Abstract

Diabetes is a widely known disease, which afflicts millions of people annually and is considered one of the leading culprits of mortality and morbidity worldwide. Researchers are making an enormous effort to propose more efficient remedies for the better amelioration of the disease. On the other hand, the public interest in the consumption of herbal medicine for therapeutic purposes is rocketing and the use of these drugs is becoming ubiquitous. *Murraya koenigii* MK is a tropical tree, originally found in the Indian subcontinent, which is an indispensable piece of the Indian diet and has multipotent medicinal capabilities. The variety of its leaves' hypoglycemic characteristics has been investigated via human, animal, and *in vitro* studies. This review intends to elaborate on the latest knowledge about the anti-diabetic and hypoglycemic effects of MK in the hope of easing the further application of MK in the alleviation of the diabetes signs and symptoms.

Keywords: Diabetes mellitus; *Murraya Koenigii*; Medicinal plant

Introduction

Diabetes mellitus is the 9th leading cause of death, with more than 1 million victims annually, and also known as the 7th top disease in terms of disability adjusted life years DALYs.[1] Diabetes mellitus type 2 prevalence was estimated to be more than 500 million in 2018 and continues to increase to 629 million by 2045.[2,3] The prevalence of undiagnosed diabetics varies from one third to more than 50% among 18-99 year old diabetic adults in different populations.[4] Despite global rising, the prevalence of the disease reflecting geographical variations, demonstrate higher rates in developed countries like Western Europe, Pacific ocean island nations, and ethnicities with the western lifestyle, although about 79% of adult patients living in low and middle income countries.[1,3,5] Diabetes mellitus type 2 is more common among wealthy people in low and middle income countries and poor people in high income countries.[6] Although type 2 diabetes is constantly increasing in children and adolescents, most diagnosed diabetics are 45-64 years old.[7,8]

Various risk factors can be involved in developing diabetes type 2, including obesity and overweight the major factor, physical inactivity, age, family history, socioeconomic status SES, genetic factors >400 genetic variants, metabolic disorders, diet, smoking, lifestyle, medications, anthropometry and infant birth weight, psychosocial factors, environmental factors pollution, radiation, etc., alcohol consumption, sleep quality and quantity, etc.[9-12]

Diabetes type 2 is mainly caused by insulin resistance and reduced insulin secretion from pancreatic β cells β cell dysfunction.[9,13] In the presence of insulin resistance and proper function of β cells, normal glucose tolerance is reached by elevated insulin secretion; therefore, insulin secretory defects are necessary for hyperglycemia.[13-15] Elevated glucose production by the liver, decreased glucose uptake by muscles and adipose tissue, and central nervous system dysfunction all arise from insulin resistance.[16] Increased glucagon secretion by α cells, elevated renal glucose reabsorption, lipotoxicity, gastrointestinal issues, and incretin dysfunction can be mentioned as other pathophysiological causes.[16,17]

The Role of Herbal Medicine in Treatment of Diabetes

Uncontrolled blood sugar in diabetic patients might have a devastating effect on most body organs. In the eye, microvascular changes lead to ischemia, macular edema, and retinal vascular leakage, a condition named "diabetic retinopathy".[18,19] Renal function can be impaired in diabetic patients due to structural changes in the glomeruli glomerulosclerosis and other injuries such as tubulointerstitial fibrosis.[20,21] Diabetic dyslipidemia might give rise to conditions like secondary atherosclerosis and consequent hypertension.[22] As a result, the risk of cardiovascular events such as heart failure and coronary artery disease becomes high in a hyperglycemic state.[23] Also, some studies have demonstrated that poor control of blood sugar in

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diabetic people increases the risk of stroke.[24] To prevent these complications, blood sugar should be lowered with various treatments.

Several drugs have been discovered and used to lower blood sugar in people with diabetes. The best known of these drugs is insulin. This hormone is applied in people whose pancreatic beta cells have been attacked by the immune system all patients with type 1 diabetes and 5 to 15% of patients with type 2 diabetes.[25] Type 2 diabetes medications usually function through mechanisms such as improving insulin secretion, stimulating its function, or reducing hepatic glucose production.[26] Some of these drugs include metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, SGLT2 inhibitors, glucagon like peptide 1 receptor agonists, and thiazolidinediones.[27] Some of these may cause complications for patients. Signs of congestive heart failure and fluid retention have been observed in a group of patients treated with thiazolidinediones.[28] Many trials have reported weight gain as two major complications of sulfonylureas or metformin.[29,30] According to former studies, dipeptidyl peptidase 4 inhibitors might result in acute pancreatitis in some diabetic people.[31,32]

Using herbal medicine to treat various diseases has long been common in different people all around the world. The multiple effects of these medicinal plants and the compounds extracted from them have been evaluated in many studies. Some of these studies have tested the anti-diabetic effect of such treatments. Cinnamon is a plant known to have an impact on lowering blood sugar or treating the complications of diabetes, such as inflammation and high blood pressure, in various animal and human studies.[33,34] Recently, the anti-glycemic effect of saffron has also been reconsidered 35. Since India has a long history of using various medicinal plants in its routine diet, many experiments are being performed on native plants of the region to assess their impacts on reducing blood sugar.[36] Some of those include Ficus religiosa [37], Eugenia jambolana 38, Momordica charantia [39], *Ocimum sanctum* [40], Trigonella foenumgraecum [41], and *Murraya koenigii* MK [42]. Here in this article, we are going to review the studies reporting on the anti-diabetic potential of *Murraya koenigii* Curry leaf, one of the most famous Indian medicinal plants.

Anti-diabetic Potential of *Murraya Koenigii*

***In vitro* studies**

Gupta et al. in their study, examined the aldose reductase inhibitory potential of alkaloidal extracts and hydroalcoholic of MK, *Piper nigrum*, *Argemone Mexicana*, and Nelumbo nucifera in terms of their IC50 value.[43] Amongst the hydroalcoholic extracts, the highest aldose reductase inhibitory activity was shown by P. nigrum, MK, A. Mexicana, and N. nucifera sub-sequently. Among the alkaloidal extracts, A. Mexicana revealed the highest inhibitory activity, followed by N. nucifera, P. nigrum, and MK. It could be concluded that the alkaloidal extracts of selected plants are strong reductase inhibitors and might be used in diabetes related complications associated with increased reductase activity such as neuropathy, retinopathy, nephropathy, and cataracts.[44,45] Postprandial hyperglycemia PPHG is one of the complications of diabetes. Glucosidase inhibitors, especially the inhibitors of α-amylase are a class of compounds that contribute to the management of PPHG. In a study conducted by Bhat et al. six ethnobotanically known plants with anti-diabetic effects were investigated for their ability to inhibit glucosidase activity *Azadirachta indica*; MK; *Ocimum tenuflorum*; *Syzygium cumini*; *Linum usitatissimum*, and *Bougainvillea spectabilis*. The results revealed that the inhibitory effect of α-amylase in chloroform extracts of *O. tenuiflorum*, *B. spectabilis*, MK, and *S. cumini* was considerable. The results also demonstrated a good inhibition of murine pancreatic and intestinal glucosidases by three extracts of *O. tenuiflorum* and chloroform extract of MK in comparison with acarbose. According to Gul et al., MK is also a source of natural antioxidants and has radical scavenging capacity as well as α-glycosidase inhibitory property.[46] Nooron et al. aimed to evaluate the effects of *Mahanine*, a carbazole alkaloid from MK with several known biological activities such as anti-tumor, anti-inflammatory, antioxidant, and anti-diabetic activity, on glucose uptake and glucose transporter 4 GLUT4 translocation in skeletal muscle cells and adipocytes.[47] They concluded that through increasing the Akt signaling pathway's activation *Mahanine* increased plasma membrane GLUT4 content and glucose uptake. Table 1 summarizes the anti-diabetic effect of MK in *in vitro* studies.

Table 1: *In vitro/In vivo studies on the anti-diabetic potential of MK*

***In vitro/ in vivo* studies**	**Results**	**References**
Swiss albino rats (150 g average weight) given 250-500 mg/kg and more bodyweight of the MK extract in different groups.	No effect on hematology or heart and lung-related organs. Acute doses (>500 mg/kg) reduced glucose and urea.	Adebajo et al. [48]
Adult male rat in 5 groups given 200-400 mg/kg MK	Bodyweight and blood glucose level were significantly reduced ($p<0.001$). Diabetes-induced tissue injury in the pancreatic islets and kidneys was reduced	Al-Ani et al. [49]

Male albino Wistar rats with streptozotocin induced diabetes with male albino Wistar rats with streptozotocin induced diabetes	A significant reduction in the levels of blood glucose, glycosylated hemoglobin, Vitamin E, ceruloplasmin, plasma and pancreas thiobarbituric acid reactive substances with a concomitant rise in the levels of insulin, Vitamin C and reduced glutathione	Arulselvan et al. [50]
Male albino wistar rats (average 170 g) given Oral administration of ethanolic extract of MK (200 mg/kg/b.w./day for 30 days)	There was a significant reduction in blood glucose, urea, glycosylated hemoglobin, uric acid, and creatinine after the treatments. An increase in insulin level was reported.	Arulselvan et al.[51]
Male swiss mice (6-8 weeks, average 25 g) given an injection of streptozotocin (3 mg•(25 g body mass)–1)	Blood glucose level and body mass were reduced after 30 days.	Dusane et al. [52]
	MKC was able to decrease the fasting glucose levels, restore the G6PD enzyme activity, inhibit the pancreatic and intestinal glucosidase, normalize plasma insulin and C-peptide levels and increase hepatic and muscle glycogen storage.	
Effect of olive leaves and Curry on blood glucose level in STZ-induced diabetic rats in doses of (OL-4, OL-8, ML-4, ML-8)	Significant decrease in blood glucose levels in 13 days of the experiment	El Amin et al. [60]
Effect of MK and BJ diet on serum glucose levels and weight gain and renal-enlargement and polyuria and UAE levels and creatinine levels	MK and BJ reduced serum sugar of STZ, but no change in body weight and renal-enlargement and polyuria and UAE levels, but BJ treatment reduced creatinine levels significantly.	Grover et al. [61]
Effect of ethanolic extract of MK in diabetic rats at doses of 200 mg/kg and 400 mg/kg	MK extract reduced blood	Husna et al. [42]
	glucose levels, body weight,	
	MDA, HOMA-IR index	
	But increased GSH, ALT levels	
Effect of mahanimbine in HFD and NPD fed mice at both doses of 2 mg/kg, 4 mg/kg.	Mahanimbine increased serum HDL levels, FFA levels, glucose tolerance, hepatic GLUT-4 gene expression, hepatic glutathione (GSH) levels, and hepatic total cholesterol (TC) levels and reduced food efficiency, HFD-induced weight gain, triglyceride levels, liver triglyceride accumulation, hyperleptinemia, Visceral fat pads, Oxidative stress indicators, hepatic TBARS, dietary triglyceride absorption	Jagtap et al. [53]
Antihyperglycemic effect of aqueous leaf extract of MK in both normal and diabetic rabbits in doses of 200,300 and 400 mg/kg	MK extract reduced blood glucose level (BGL)	Kesari et al. [62]
Alloxan-induced diabetes in adult male Wistar rats (150-200 g each) given aqueous leaf extract of MK at doses of 100 mg/kg, 150 mg/kg and 200 mg/kg body weight, and normal saline for the control group	Significant dose-dependent hypoglycemic effect of MK on diabetic induced rats, while unremarkable results in healthy animals	Lawal et al. [63]
	The less substantial effect of MK in comparison with chlorpropamide	

Albino Wistar rats (200-250 g each) divided into one control group (given 0.1 M cold citrate buffer) and 3 STZ afflicted diabetic groups given MK (200 mg/kg body wt/day), glibenclamide (0.6 mg/kg body wt/day) and normal saline for 30 days	Significant reduction in blood glucose from day 7 to 28 in the diabetic MK group, and eventually reaching one-third of the baseline fasting measurements. Similar changes in the diabetic glib group. MK was more effective than glibenclamide in counteracting the effect of STZ	Sudha M J et al.[64]
Adult male Wistar rats (weighing 200 ± 20 g) afflicted with STZ (70 mg/kg, ip) divided into three groups: one healthy untreated group which was given distilled water and two others which were allowed a single administration of the polyherbal drug at doses of 0.25, 0.5, 1.0,1.5, and 2.0 g/kg and followed up for 14 days	Hot water and acetone (water) extract of the drug, at the doses of 1.0 and 1.5 g/kg ($p< 0.05$), significantly reduced the blood glucose of the diabetic rats. Such effect was not observed among healthy untreated rats	Liyanagamage et al.[65]
STZ-treated male albino Wistar rats (weight: nearly 160-180 g) given 150 mg/kg per day MKLEe aqueous extract orally for 30 days	Remarkable decline in the levels of blood glucose, glycosylated hemoglobin and urea, with a simultaneous rise in glycogen, hemoglobin and protein amelioration of glucose tolerance and an increment in insulin and C-peptide levels	Narendhirakannan et al. [66]
Swiss albino male mice (age:7-8 weeks, weight: 20–25 g) were provided with an intramuscular injection of 1 mg/kg dexamethasone and divided into five groups: one control group given 10 g/L gum acacia and four other receiving dexamethasone alone (Dexa-control) or dexamethasone along with metformin (250 mg/kg) or two distinct doses of MK (100 and 250 mg/kg, respectively)	MK yielded a reduction in insulin resistance and enhanced glucose tolerance. MK triggers glucose uptake in L6 skeletal muscle cells by increasing the GLUT4 receptors on the cell membrane, which is directly manipulated by AKT phosphorylation pathway	Pandey et al.[55]
In vitro study utilizing L6-GLUT4myc Myotubes and assessment of 6 distinct carbazole alkaloids of MK on glucose uptake.	Compounds number 2-5 had significant effects in lowering blood glucose in STZ-induced animal model of diabetes	Patel et al.[67]
In vivo study using both STZ-afflicted diabetic rats and db/db mice which were given compounds 1-6 at doses of 100 mg/kg body weight	Compounds 3 and 4 had a remarkable hypoglycemic effect in comparison with metformin. Koenidine triggered AKT-dependent signaling pathway and increased in GLUT4 translocation in L6-GLUT4myc myotubes.	
Male Swiss albino mice (weight:20-26 g) were injected with alloxan monohydrate intraperitoneally as a model of diabetes and provided with 50% methanol extract or aqueous extract of MK.	MK extracts (AEM and MEM) could reduce fasting blood glucose, total cholesterol, triglycerides, and phospholipids.	Paul et al.[68]
	AEM, as opposed to MEM, was more efficient in yielding the results above	
Swiss albino mice (weight: 18-20 g) were injected with STZ intraperitoneally at the dose of 200 mg/kg of body weight and administered with MK extract at doses of 75 and 150 mg/kg of body weight for 15 days.	MK extracts were efficient in lowering blood sugar and when administered at 150 mg/kg of body weight, the efficacy was higher.	Saha et al.[69]
STZ-induced male Wister rats (70 mg/kg) given MK (300 and 500 mg/kg p.o.)	Reduction in the blood glucose level as well as the level of glycosylated hemoglobin,	Tembhurne et al.[56]
	significant increase in the grip strength as well as pain perception more effectively than standard glibenclamide	

STZ-induced male Wister rats (70 mg/kg, intravenously) given MK extract (300 and 500 mg/kg) and glibenclamide 13 days after single-dose STZ and cisapride or vitamin E from the last week (8th week) of experimentation	Significant decrease in the blood glucose level, increase in the gastrointestinal motility as a result of defending against cholinergic neurons' peripheral damage by providing antioxidant shelter	Tembhurne et al.[57]
Alloxan-induced male and female rats of Sprague-Dawley strain given aqueous extract (600 mg/kg b.wt.) and methanol extract (200 mg/kg b.wt.) of MK	Significant decrease in the blood glucose level, a significant increase in the plasma insulin level.	Vinuthan et al.[58]
Male ob/ob mice given MK extract (80 mg/kg)	A decrease in the blood glucose level as well as body weight	Xie et al. [70]
Alloxan-induced or STZ-induced male and female Albino rats (alloxan 35 mg/kg or STZ 60 mg/ kg) given a different diet containing MK powder (5, 10, and 15%)	A decrease in the blood glucose level in mild diabetic rats (alloxan-induced), which was dose-dependent, an insignificant reduction in the blood glucose level in moderate diabetic rats (STZ -induced)	Yadav et al.[71]
Fructose-induced male rats of Sprague-Dawley strain given MK (in a ratio of 15% of total fructose diet)	No effect on the blood glucose level as well as plasma insulin level	Yadav et al.[72]
STZ-induced male rats of Sprague-Dawley strain (70 mg/kg) given a different aqueous extract of MK (200 and 400 mg/kg body weight/day for 30 days)	Significant decrease in the serum urea and creatinine level, which was dose-dependent,	Yankuzo et al. [59]
	considerable increase in PAC level as well as GPx level, tissue regeneration in damaged kidneys	
Aldose reductase inhibitory extract of	Among the hydroalcoholic extracts, the highest inhibitory activity was shown by P. nigrum aldose reductase (IC50 value 35.64 ± 2.7 μg/mL) and then by M. koenigii (IC50 value 45.67 ± 2.57 μg/mL), A. Mexicana (IC50 value 56.66 ± 1.30 μg/mL), and N. nucifera (IC50 value 59.78 ± 1.32 μg/mL).	Gupta et al. [44]
Piper nigrum, MK, *Argemone mexicana*, and	A. mexicana (IC50 value 25.67 ± 1.25 μg/mL) Among the alkaloid's extracts were shown to have the highest inhibitory activity. Followed by N. nucifera (IC50 value 28.82 ± 1.85 μg / ml), P. nigrum (IC50)	
Nelumbo nucifera	1.63 ± 1.30 μg / ml) and then M. koenigii (IC50 value) 35.66 ± 1.64 micrograms / ml).	
Amylase inhibitory effect of *Azadirachta indica* Adr. Juss.; MK (L.) Sprengel; *Ocimum tenuflorum* (L.) (syn: Sanctum); *Syzygium cumini* (L.) Skeels (syn: Eugenia jambolana); *Linum usitatissimum* (L.)	In the chloroform extract of O. tenuiflorum;	Bhat et al. 43
Bougainvillea spectabilis.	*B. spectabilis*; MK and S. cumini, the inhibitory effect of α-amylase was significant.	
	The results showed promising inhibition of murine pancreatic and intestinal glucosidases by the three extracts of *O. tenuiflorum* and chloroform extract of MK in comparison with acarbose.	
Antioxidant and α-glycosidase effect of MK leaf extracts (MKA & MKW)	MKA and MKW extracts had more effective antioxidant and radical inhibition activities in comparison with other extracts	Gul et al. [46]

The effects of *Mangifera indica*, which contains mangiferin (xanthon), and the leaves of MK, which contain mahanimbine (carbazole) on glucose utilization in 3T3-L1 cells	Treatment of 3T3-L1 cells with mangiferin and mahanimbine increases glucose utilization in a dose-dependent manner. At a concentration of 1 mM, manganiferin did not treat a 2-fold increase in glucose intake than the control. In the case of mahanimbine, the effect observed in 1 mm was approximately equivalent to a positive control (insulin at one μM).	Kumar B et al. [73]
Effects of *mahanine*, a carbazole alkaloid from MK, on adipocyte cells	*Mahanine* induced Akt-activation was reversed by treatment with wortmannin, an Akt inhibitor. Furthermore, it was found that *mahanine* particularly increased GLUT4 translocation to the plasma membrane in L6 myotubes.	Nooron et al. [47]

MK, *Murraya Koenigii*; MKC, *Murraya Koenigii* chloroform extract; G6PD, Glucose-6-phosphate dehydrogenase; STZ, streptozotocin; OL, *Olea europaea*; ML, *Murraya Koenigii*; BJ, *Brassica juncea*; MDA, Malondialdehyde; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; GSH, glutathione; ALT, Alanine transaminase; HFD, high fat diet; NPD, normal pellet diet; HDL, high-density lipoprotein; FFA, Free Fatty Acid; GLUT, Glucose Transporter; TBARS, Thiobarbituric acid reactive substances; MKLEe, M. koenigii leaf ethanol extract; AKT, Protein kinase B; AEM, aqueous extracts of *Murraya koenigii*; MEM, methanol extracts of *Murraya koenigii*; PAC, plasma antioxidant capacity; GPx, glutathione peroxidase; MKA, *Murraya Koenigii* ethanol extract; MKW, *Murraya Koenigii* water extract

Animal studies

Several *in vivo* studies have demonstrated the anti-diabetic potential of MK. Adebajo et al. designed a study to evaluate anti-trichomonal, biochemical and toxicological effects of MK extracts on Swiss albino rats. Acute administration of the extracts resulted in a significant reduction of blood glucose level and increase of serum cholesterol, while chronic administration for 14 days had reduction effects on both, suggesting that MK might have hypoglycemic outcomes after prolonged application.[48] In a study performed by Al-Ani et al. the potential anti-diabetic effects of *Murraya koenigii* aqueous extract were explored.[49] They established that STZ induced diabetic rats treated with MK showed a significant reduction in fasting blood glucose levels without any regard to the dose of administrated extract. The mentioned extract also reduced diabetes induced tissue injury in the pancreatic islets and kidneys. All the above observations highlighted that MK aqueous extract might have beneficial impacts to prevent cellular oxidative damage in Sprague Dawley rats with streptozotocin induced diabetes.

In 2006, a study investigated the potential antioxidant impacts of *Murraya koenigii* leaves' extract against pancreatic β-cells damage.[50] As expected, oral administration of leaves extract tended to bring altered variants back to near control levels. MK yielded a significant reduction in the levels of blood glucose, glycosylated hemoglobin, Vitamin E, ceruloplasmin, plasma and pancreas thiobarbituric acid reactive substances TBARS. Additionally, a significant increase in activities of pancreatic superoxide dismutase, catalase, and glutathione peroxidase was observed, which can be interpreted as positive effects of MK on the cellular antioxidant defense system. Transmission electron microscopic studies also supported the protective outcomes of MK on pancreatic β-cells. From the results obtained, it is implied that MK might exhibit antioxidant as well as anti-hyperglycaemic activity. An *in vivo* study was conducted by Arulselvan et al. evaluated the Anti-diabetic effects of MK leaves on diabetes induced male albino Wistar rats.[51] Samples were taken after oral administration of MK's ethanolic extract; insulin levels, glycosylated hemoglobin, blood sugar, creatinine, uric acid, and urea were determined. All the calculated values showed a decrease except for the level of insulin, which was increased. These outcomes demonstrated that MK could possess remarkable hypoglycemic potential in diabetes induced rats. Dusane et al. studied antidiabetogenic effects of MK on STZ induced diabetic male Swiss mice in search of a safe and less toxic alternative drug for diabetes treatment. It was able

to decrease the fasting glucose levels, restore the G6PD enzyme activity, inhibit the pancreatic and intestinal glucosidase, normalize plasma insulin and C-peptide levels, and increase hepatic and muscle glycogen storage.[52] MK was even capable of maintaining glucosidase inhibition after discontinuing the treatment, suggesting its possible long term effects. In this study, MK effects on pancreatic b-cell protection were also reported for the first time. Altogether, these findings suggested that MK extracts can be a potential candidate for diabetes treatment.

Jagtap et al. tried to apply mahanimbine major carbazole alkaloid from MK in Normal pellet diet NPD and high fat diet HFD fed mice.[53] The results revealed that mahanimbine significantly reduced food efficiency, HFD induced weight gain, triglyceride levels, liver triglyceride accumulation, hyperleptinemia, visceral fat pads, oxidative stress indicators, and dietary triglyceride absorption in treated mice during the study. Nevertheless, mahanimbine administration had a rising effect on serum HDL levels, serum-free fatty acid levels, glucose tolerance, hepatic GLUT-4 gene expression, hepatic glutathione levels, hepatic total cholesterol levels in 12 weeks of the experiment. Kesari et al. performed a study by applying aqueous extract of MK in diabetic rats.[54] A notable reduction in fasting blood glucose FBG level was illustrated. Even so, no marked change was recorded in FBG of medicated normal rats during 30 days of the experiment. In addition, administration of aqueous MK decreased total cholesterol level, triglyceride level, LDL, and VLDL levels. However, HDL cholesterol level was built up in medicated normal and diabetic rats compared with their parallel control group. Interestingly, the body mass of treated diabetic rats was close to the normal range and no urinary sugar was determined in comparison with the diabetic control group during 30 days of study. Considering all the above, it is implied that MK might be useful as a spice for daily management of diabetes mellitus, yet it cannot replace the conventional anti-diabetic treatments. The impact of MK consumption on insulin resistance in a simulation of diabetes exerted on dexamethasone injected rats has also been investigated.[55] As expected, MK yielded a reduction in insulin resistance depicted by an enhancement in glucose tolerance and insulin provoked AKT phosphorylation in skeletal muscles. They also declared that MK triggers glucose uptake in L6 skeletal muscle cells by increasing the GLUT4 receptors on the cell membrane.

The efficiency of MK in diabetic related complications has also been studied. According to the study performed by Tembhurne et al., the MKL treatment of diabetic neuropathy developed in STZ induced male Wister rat indicated beneficial effects on decrease in the glycemic level as well as protecting animals against diabetic neuropathy development.[56] The results proved an increase in the grip strength of diabetic rats, while the animals indicated a later grip strength decrease developed by neuropathy induction. The pain sensitivity results noted an increase in each of licking time, withdrawal latency in hot plate, and tail flick tests, which suggests the existence of pain perception and nerve damage prevention. The results also suggested a major decrease in glycosylated hemoglobin level after chronic MKL treatments comparable to glibenclamide. Tembhurne et al. also suggested that MKL extract had a protective effect on male adult Wistar rats with STZ induced diabetes against gastrointestinal disorders by decreasing the glucose level in blood as well as increasing the gastrointestinal motility, which was correlated to the increase in the activation of percent response to acetylcholine in distal colons and the decrease of TBARS as an index of oxidative stress in intestines.[57] Vinuthan et al. demonstrated that daily oral consumption of aqueous and methanol extracts of MK leaves not only exhibited a progressive, significant reduction in blood glucose level of alloxan induced diabetic rats of Sprague Dawley strain as compared to diabetic control groups but also resulted in a significant rise in the insulin level of plasma.[58] Due to alloxan's destructive effect on beta cells of the pancreas inducing hyperglycemia, it can be concluded that the hypoglycemic effect of curry leaf may be induced as a result of insulin synthesis stimulation and/or its secretion from pancreatic beta cells.

Yankuzo et al. investigated the effects of MK leaves on the management of diabetes induced renal impairment. Daily oral consumption of different doses of aqueous extract of MK leaves resulted in a significant dose dependent reduction in serum creatinine and urea as well as an increase in plasma antioxidant capacity levels in streptozotocin induced diabetic Sprague Dawley strain rats leading to elevation of GPx Red blood cells glutathione peroxidase level.[59] Moreover, Histological examination of these animals' kidneys indicated tissue regeneration by the aqueous extract treatment. Thus, this study suggested that MK leaves' treatment might have beneficial effects in preventing renal micro-vascular damage caused by hyperglycemia induced oxidative stress through its potential antioxidant effect. Table 1 summarizes the anti-diabetic effect of MK in *In vivo* studies.[60-73]

Human studies

The anti-diabetic potential of MK has also been studied on humans. In a study by Anuruddhika et al. the effect of 14 different leafy porridges of MK on ten healthy individuals' blood sugar was evaluated.[74] The glycemic index and peak blood glucose of the participants were calculated. The results demonstrated that 13 types of porridges had a low glycemic index <55. A reduction of more than 25% in peak blood glucose was also reported in the porridges of 12 plants. Based on these findings, it was concluded that these porridges could be used as breakfast in diabetic patients to prevent severe blood sugar fluctuations during the day. A study conducted by Iyer et al. tried to investigate the effect of MK leaf powder on blood sugar in dia-

betic patients.[75] The results showed that fasting blood sugar on the 15th day significantly decreased compared to the first day, while this decrease in 2 h prandial blood sugar was not significant. On the 30th day, a slight decrease was observed in both variables than on the first day. Kirupa et al. also designed a randomized controlled trial to assess curry leaf powder's hypoglycemic effect in type 2 diabetic patients on oral hypoglycemic medications.[76] Fasting and postprandial blood glucose levels were measured before and after the food and curry powder consumption. Unlike the diabetic control group, the diabetic experimental group showed a remarkable decrease in fasting and postprandial glucose levels after 30 days. A significant reduction of pre and post-lunch glucose levels was seen. The hypoglycemic effect of curry leaf powder was demonstrated in this study. Moreover, in 2010, Pirasath et al. investigated the effect of dietary curries on the glycemic index GI in 20 healthy 20-24 year old volunteers.[77] The GI was calculated for different foods in combination with green leaf curry, the gravy of soya meat, or both by measuring the blood glucose level 2 hours after consuming the food containing 75 g carbohydrates. The study showed adding curries to food lowered their glycemic index. Therefore, its consumption should be considered in people with diabetes. Table 2 and Figure 1 summarize the anti-diabetic effect of MK in human trials.

Figure 1: *Curry Leaf s Anti-diabetic potential and underlying mechanisms in human and animal.*

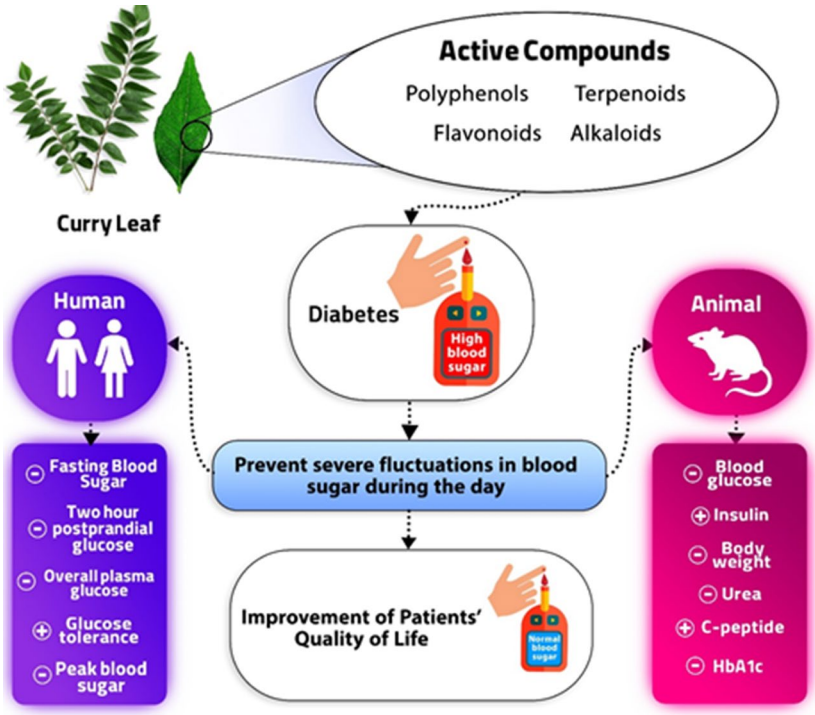

Table 2: *Clinical (human) trials of the anti-diabetic potential of MK*

Human trials/dosage	Results	References
Ten healthy individuals (25 to 30 years old, BMI between 18 to 25 and fasting blood sugar below 110) fed with a standard diet (25 g glucose + 250 cc water) and leafy porridge of MK (350 – 400 g consists of 25 net carbohydrates)	Glycemic index was low (44), and a 35% reduction was observed in peak blood sugar	Anuruddhika et al.[74]
Thirty patients with non-insulin-dependent diabetes mellitus treated with two packages of 6 g of MK leaf powder per day (one of them with lunch and the other with dinner) in one month	Significant reduction in fasting blood sugar after 15 days (about 18 mg/dl), a slight decrease in fasting and 2 h-prandial blood sugar after 30 days compared to the beginning of the study	Iyer et al.[75]
Ten type 2 diabetic men (51-62 years) given 15 g of curry leaf powder per day for consumption with lunch over 30 days.	Significant reduction of fasting and postprandial glucose levels, pre-lunch and post-lunch glucose level, and blood glucose load	Kirupa et al.[76]

Twenty healthy 20-24-year-old volunteers were given 75 g of glucose and 75 g of carbohydrates containing curry leaf, soya meat, or both after fasting overnight on different days, glycemic index (GI) of different carbohydrates in combination with test foods and blood glucose level after 30 minutes were measured.	Significant reduction of GI values of carbohydrates in combination with green leaf curry ($p<0.05$)	Pirasath et al.[77]

BMI, body mass index; MK, *Murraya Koenigii*; GI: glycemic index

Conclusion

Despite a life-long endeavor in finding a definite treatment for diabetes and regardless of all the progress we have made, the journey has not come to an end. As to the growing inclination to herbal medicine, several studies have reported the potential anti-diabetic and hypoglycemic effects of MK leaf extracts in human or animal models. In addition, the efficacy of MK extracts in diabetes models was compared to some established drugs in diabetes. MK was found to have a satisfactory impact on glucose level, lipid profile, oxidative stress levels and several more diabetes associated markers and have manifested itself as a promising agent to be used as an adjuvant to diet or consumed as a drug at certain doses. Hereby, we have gathered and discussed some of the most remarkable investigations in this topic to provide a better under-standing for the researcher.

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