

Review Article

A Review of Anti-hyperglycemic Effects of Curry Leaf Tree (*Murraya koenigii*)

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Abstract

Diabetes mellitus is becoming a metabolic disease that is defined by the level of hyperglycemia. Nowadays, it has a serious threat to public healthiness in throughout the world. Constituents and extracts isolated from diverse natural resources, mainly plants, have constantly been a rich store for controlling and treating diabetes problems. Numerous researches are ongoing to identify the suitable traditional medical drugs, medicinal herbs, and resources for managing this condition. *Murraya koenigii* Spreng (family Rutaceae) is commonly known as a 'curry leaf tree' locally. It is widely scattered in India and Sri Lanka, and leaves are commonly used for cooking. And also mainly used for various health conditions such as diabetes, anemia, diarrhea, and others. The present review aimed to critically review the anti-hyperglycemic effect of the *M. koenigii* based on the review, *in vitro*, *in vivo*, and clinical studies. Based on this review, the *M. koenigii* possess flavonoids, phenols, saponins, alkaloids, tannins, and cardiac glycosides. It has shown a potential anti-hyperglycemic effect on induced diabetic rats. This review reported the potential of *M. koenigii* and its extract to be a high-value dietary product in terms of its anti-hyperglycemic effects and industrial profits. Therefore, the present review supports the researchers and readers/users to realize the importance of using *M. koenigii* in managing diabetes mellitus. Further, this review provides a valuable document for future scientific-related clinical trials in diabetic patients.

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INTRODUCTION

Diabetes is a metabolic condition primarily demarcated by the level of hyperglycemia, giving rise to a risk of microvascular damage. It is related to reduced life expectancy, significant morbidity due to specific diabetes interconnected microvascular problems, increased risk of macrovascular impediments, and reduced quality of life¹. It is a global disease found in all nations of the world. In the last two to three decades, there has been an explosive upsurge in people with diabetes². According to World Health Organization, about 422 million people in low-and middle-income countries have diabetes, and 1.6 million deaths occur due to diabetes each year³. Many herbal remedies are used in many countries to control and manage diabetes mellitus. Commonly, these medicinal herbs effectively manage the diabetic condition for a long time due to their various biological constituents, such as saponins, glycosides, polysaccharides, flavonoids, alkaloids, and terpenoids, which are possessed anti-diabetic activities⁴. Several *in vitro* and *in vivo* studies have been supported in recent years showing the potential effects of curry leaf tree or *Murraya koenigii* Spreng (family Rutaceae) therapies and improved blood glucose control to manage the diabetic condition. This tree is commonly known as sweet neem and is distributed throughout tropical zones and widely used for various health issues such as diabetes, diarrhea, anemia, ulcer, obesity, inflammation, and others, in the traditional medical system of Sri Lanka^{5,6}.

Therefore, the present review was to aim to do a critical review of the antihyperglycemic effect of *M. koenigii* based on reviews, *in vitro*, *in vivo*, and clinical studies from all available sources such as past and recent traditional textbooks, research articles, original research papers, websites, reputed scientific databases and other related documents during the year of 2021 at Jaffna District, Sri Lanka. This review article will be valuable to the documented indication of the antihyperglycemic special effects of *M. koenigii*.

CLASSIFICATION OF MURRAYA KOENIGII

Classification and common names of *M. koenigii* presented in Table I.

Table I. Classification of *M. koenigii*

Classification	Identity
Domain	Eukaryote
Kingdom	Plantae
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta
Superdivision	Embryophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Superorder	Rosanae
Order	Sapindales
Family	Rutaceae
Genus	<i>Murraya</i> J. Koenig ex L.
Species	<i>Murraya koenigii</i> (L.) Spreng.
Common Name	Karapincha
English Name	Curry Leaf Tree
Sanskrit Name	Girinimba, Krishnanimba
Tamil Name	Kariveppilai
Hindi Name	Currypatta

DISTRIBUTION OF MURRAYA KOENIGII

Murraya koenigii tree is a tropical to a subtropical tree distributed and cultivated throughout India, and it can be found in moist forests in Bhutan, Nepal, Pakistan, Sri Lanka, Thailand, Vietnam, and Laos. Its propagation is done by seeds⁸.

MORPHOLOGY OF MURRAYA KOENIGII

Macroscopical features

It is a semi-deciduous aromatic shrub or small tree which is about 2.5 m up to 6 m in height and 15-40 cm in diameter with a short trunk, thin, smooth grey or brown bark (Figure 1). The leaves are imparipinnate, glabrous, and very intensely aromatic and about 30 cm long, each bearing 9-25 leaflets, short-stalked, alternate, and have a reticulate venation. Flowers are small, white funnel-shaped, fragrant, bisexual, calyx deeply five clefts, and pubescent. Petals five, free, whitish, glabrous, and with dotted glands. Fruits occur in close clusters, small, round to oblong in shape, glandular, thin pericarp enclosing one or two seeds having spinach green color^{9,10}.

Microscopical features

Murraya koenigii shows the presence of unicellular trichomes with obliterated lumen, parenchymatous pith in the petiole, long pericyclic fiber in the midrib, large cruciferous stomata, and prismatic calcium oxalate crystals^{11,12}. The root shows tetrarch to pentarchy stele, phelloderm fibers are absent, and concentric grains of parenchyma is present. Powder of *M. Koenigii* are green in color with no distinct odor or taste, unicellular, curved trichomes, two-layered palisade, a portion of secretory canals, well-developed pericyclic fibers, and a few crystals of calcium oxalate are the important categorizing

characters¹³. *Murraya koenigii* powder fluoresces brownish-black. When treated with 1 N methanolic sodium hydroxide, the powder illustrates yellowish-white color and, when mounted in nitrocellulose, produces chocolate fluorescence^{14,15}.



Figure 1. Different parts (a: leaves; b: flowers; c: seeds; d: fruits; e: powder; f: juice) of *M. koenigii*

GROWING SEASON OF MURRAYA KOENIGII

This plant has flowers and green leaves during the spring, summer, and rainfall. The leaves drop off during their' resting period in the winter. They like full sun and well-drained soil, which should be the dry side, and they need fertilizer in the month of summer^{16,17}. The fruiting season is from the end of June to the end of August, and July is considered the peak fruiting season. This plant can grow to a tree up to 6 m tall in warm, humid climates, but it can also be grown up very successfully in a pot as a much smaller plant^{18,19}.

LITERATURE REVIEW STUDIES

The plant has main constituents such as caryophyllene, terpene, carvomenthone, menthol, menthone, citral, and linalyl acetate, which contribute to the flavor²⁰. Leaves, seeds, flowers, and fruit of *M. koenigii*, contain constituents responsible for a variety of numerous biological processes²¹. A review study mentioned that traditionally *M. koenigii* leaves are used in Ayurveda medicine to manage diabetes, and mahanimbine is a carbazole alkaloid present in leaves, stem bark, and root of *M. koenigii* has a beneficial effect in the controlling the diabetes mellitus²². Another review related to the role of medicinal herbs in treating diabetes has reported that *M. koenigii* is included under the herbs of glucose-lowering effects²³. Another review study informed that the *M. koenigii* acts as an anti-diabetic due to decreases oxidative stress by acting on Paraoxonase activity with Koenimbidine, Murrayacine, and Murrayazoline chemical constituents¹¹. Qais *et al.*²⁴ informed in their review article on anti-diabetic plants that the *M. koenigii* plants showed a significant hypoglycemic effect on carbohydrate metabolism using experimental rats. Based on the numerous *in vivo* studies, some reviews stated that *M. koenigii* leaves possess statistically significant anti-hyperglycemic effects in diabetic rats²⁵⁻³⁰. Numerous review-related studies mentioned that the leaves, fruit, and fruit juice have anti-diabetic properties³¹⁻³³.

In vitro phytochemical studies

Leaves of *M. koenigii* exposed tannins in the aqueous extract and quinones, coumarin, and sugar in both the alcoholic extracts³⁴. Different fractions of ethanol leaves extract of *M. koenigii* indicated the occurrence of saponins, alkaloids, flavonoids, tannins, and cardiac glycosides³⁵⁻³⁷. Phytochemical screening exhibited the occurrence of carbohydrates, alkaloids, steroids, and flavonoids in the different extracts of the *M. koenigii* plant³⁸⁻⁴⁶. The study in India established that flavonoids, phenol, tannins, saponins, terpenoids, reducing sugar, and alkaloids are present in both urban and coastal areas of *M. koenigii*⁴⁷. The hydro-distillate essential oil of *M. koenigii* leaves showed the most potent antioxidant activity within the concentration range⁴⁸. The FRAP and DPPH assays confirmed that the highest total flavonoids and phenolic contents extracted from the curry leaf in Malaysia showed the highest antioxidant activity⁴⁹.

Phytochemicals such as flavonoids, monoterpenes, terpenoids, stilbenes, lignans, coumarins, alkaloids, and others, have been proposed as effective supplements for diabetes management and prevention of its long-term complications *in vitro* and *in vivo*⁵⁰. Further, studies have proven that various phytochemical components of anti-diabetic herbs such as flavonoids, alkaloids, saponins, tannins, and terpenes were responsible for the anti-diabetic activities of the plants, and they mentioned that the flavonoids were observed to be the most popular anti-diabetic principle among the phytochemicals⁵¹. Based on the phytochemicals related to studies of *M. koenigii* also proven that it has flavonoids in its different extracts⁵².

In vivo animal studies

Numerous comparative animal studies proved that the different extracts of the *M. koenigii* have shown anti-hyperglycemic effects in diabetic rats. Vinuthan *et al.*⁵³ found that the daily oral administration of aqueous (600 mg/kg BW) and methanol extracts (200 mg/kg BW) of *M. koenigii* for eight weeks exhibited a significant reduction ($p < 0.05$) in alloxan-induced diabetic rats when associated to control group. Another study found that the aqueous and methanol extracts of the *M. koenigii* have significantly declined the blood glucose level in streptozotocin-nicotinamide (STZ-NA) induced diabetes rats throughout 28 days of treatment⁵⁴. An animal study found that the orally administered ethanol extract of *M. koenigii* at a dose of 200 mg/kg/BW/day for 30 days exhibited a significant reduction in blood glucose levels in STZ-induced diabetic rats⁵⁵. Fauziah *et al.*⁵⁶ suggested that the treatment of ethanol leaves extract of *M. koenigii* at several doses (50% mL/10 g BW, 70% mL/10 g BW, and 90% mL/10 g BW) for 14 days of treatment significantly affected the decrease on blood sugar levels in alloxan-induced diabetic mice. Fraction (1 and 2) of ethanol leaf extract (400 mg/Kg BW) of *M. koenigii* showed significantly ($p > 0.05$) decreased blood sugar levels by 72% when compared to the group of alloxan-induced diabetic rats⁵⁵.

Lawal *et al.*⁵⁷ found that the orally administered at the various dose levels (at 100 mg/kg, 150 mg/kg, and 200 mg/kg BW), its aqueous leaf extract for seven days possessed hypoglycaemic activity in normal and alloxanized diabetic rats. Tembhurne and Sakarkar⁵⁸ mentioned that the user leaves could control body weight and maintain the glycemic levels in diabetic patients because those leaves suggested a potent hypoglycaemic activity in high-fat obese rats. Orally administered, its aqueous leaf extract (200 mg/kg BW) showed anti-hyperglycemic activity greater than glibenclamide in STZ-induced diabetic rats for 28 days⁵⁹. Al-Ani *et al.*⁶⁰ recommended that its aqueous leaf extract (200 mg/kg and 400 mg/kg) for a month exhibited significant ($p < 0.001$) enhancement in blood sugar levels against cellular oxidative damage in STZ-induced diabetic rats. El Amin *et al.*⁶¹ recommended that the orally administered aqueous extracts of *M. koenigii* show a significant ($p \geq 0.05$) anti-hyperglycemic effect (range 55.6-64.6%) compared to the metformin (62.7%). Oral administration of *M. koenigii* aqueous extract (300 mg/kg, p.o) significantly reduced the blood glucose level in the diabetic group for 28 days in alloxanized diabetic rats⁶².

Bhat *et al.*⁶³ recommended that its chloroform extract has significant inhibition (IC_{50} values of 1.96, 1.06, and 2.68 μ g/mL) with porcine pancreatic α -amylase (56.40%) as well as murine pancreatic and intestinal glucosidases as compared with acarbose. A study identified that the orally administered chloroform leaf extracts (250 and 500 mg/kg BW) for 30 days ensued in a significant reduction of blood sugar from 296.62 ± 20.12 to 80.22 ± 03.63 in alloxan-induced albino rats⁶⁴. Ahmed *et al.*⁶⁵ found that its chloroform leaves extract has shown significant antidiabetic outcomes at doses of 250 and 500 mg/kg BW in alloxan-induced diabetic albino rats on intraperitoneal injection when matched to the control group. Another study

justified the combination of *M. koenigii* leaves extract (150 mg/kg; p.o.) and *V. vinifera* seeds extract (100 mg/kg; p.o.) have shown the potential antidiabetic effect after 21 days of treatment in alloxan-induced diabetic rat⁶⁶.

Its hydroalcoholic extract treatment exhibited a significant antidiabetic effect by restoring blood glucose and HbA1C level compared to the control group in STZ-induced rats⁶⁷. A study demonstrated that feeding a diet containing various doses of curry leaves caused a maximal reduction in blood sugar in STZ-induced mild and moderate diabetic rats after seven days⁶⁸. Another study confirmed that its ethanolic extract significantly reduced blood glucose levels at both doses, 200 and 400 mg/kg BW, in STZ-NA-induced rats⁶⁹. The researchers observed that the curry leaf extract could decrease blood glucose levels from 387.0±15.6 mg/dL to 214.0±26.6 mg/dL after ten days in diabetic ob/ob mice⁷⁰. A study indicated that its aqueous extract has a favorable effect in bringing down the severity of diabetes⁶. Sudha *et al.*⁵⁹ stated that its aqueous leaf extract was superior to glibenclamide in STZ-induced diabetic rats. Its leaves in tea bags have comparable activity with glibenclamide in reducing the blood glucose levels in alloxan-induced diabetes Wistar albino rats⁷¹. A single oral administration of variable dose levels of aqueous extract of *M. koenigii* showed a marked improvement in the sub, and mild diabetic rabbits in glucose tolerance test, and they suggested that it may be prescribed for controlling diabetes mellitus⁶.

Human studies – Clinical trials

A clinical trial was conducted to assess the efficacy of *M. koenigii* leaves powder in reducing the blood glucose level of the 60 type II diabetic patients (30 participants in the experimental and 30 in the control group) in a rural area of Medavakkam, Chennai, that found that 10 g of *M. koenigii* leaves powder for 14 days along with their food showed a significant variance between the pre and post-prandial blood glucose level in the experimental group⁷². Another clinical trial found that the use of *M. koenigii* leaves juice (100 mL twice a day for seven days) has shown significantly ($p < 0.00003$) to reduce the blood sugar level among the 20 experimental groups of diabetic subjects when compared with 20 control group subjects who are above 40 years of age at selected hospitals, Puducherry⁷³. Another clinical trial reported a significant difference after the administration of *M. koenigii* leaves powder in the average fasting and post-prandial blood glucose at a 5% significance level among the diabetic patients^{74,75}. Several review studies recognized that *M. koenigii* has anti-diabetic potency due to carbazole alkaloid present in *M. koenigii*. **Table II** summarizes the results of different phytochemical, *in vitro*, and *in vivo* studies.

Table II. Summary of different studies of *M. koenigii*

Preparation / extract	Effects
In vitro studies	
Aqueous extract & alcoholic extracts	Phytochemicals ³⁴
Ethanol extract	Phytochemicals ³⁵⁻³⁷
Different extracts	Phytochemicals ³⁸⁻⁴⁸
Hydro-distillate essential oil	Antioxidant activity ⁴⁹
Aqueous extract	Antioxidant activity ⁵⁰
In vivo studies	
Aqueous and methanol extracts	Hypoglycaemic effect in alloxan-induced diabetic rats ⁵³
Methanol extract	Hypoglycaemic effect in STZ-NA induced diabetes rats ⁵⁴
Ethanol extract	Hypoglycaemic effect in STZ-induced diabetes rats ^{55,69}
Aqueous leaf extract	Hypoglycaemic effect in alloxan-induced diabetic mice ^{36,56}
	Hypoglycaemic effect in alloxan-induced diabetic rats ^{57,59,66}
	Hypoglycaemic effect in STZ-induced diabetes rats ⁵⁹⁻⁶²
	Hypoglycaemic effect in diabetic rabbits ⁶
Chloroform extract	Hypoglycaemic effect ⁶³
Hydroalcoholic extract	Hypoglycaemic effect in alloxan-induced diabetic rats ^{64,65}
	Hypoglycaemic effect in STZ-induced diabetes rats ⁶⁷
	Hypoglycaemic effect in STZ-induced diabetic rats ⁶⁸
	Hypoglycaemic effect in diabetic ob/ob mice ⁷⁰
Diet containing various doses of curry leaves	Hypoglycaemic effect in alloxan-induced wistar albino rats ⁷¹
Leaf extract	
leaves tea bag	
Human studies – Clinical trials	
Curry leaves powder	Reduce blood glucose in type II diabetic patients ⁷³
Curry leaves juice	Reduce blood glucose in diabetic patients ⁷²

The phytochemical studies demonstrated that the *M. koenigii* possess the major constituents as phenols, saponins, alkaloids, flavonoids, tannins, and cardiac glycosides, which are secondary metabolites effective for antioxidant therapy. Therefore, *M. koenigii* can act as an anti-diabetic plant to decrease oxidative stress because oxidative stress also induces diabetes from free radicals. Based on the animal studies, numerous qualified animal studies were proved that the different extracts; aqueous, methanol, ethanol, and chloroform extracts of the *M. koenigii* in different doses and different periods have shown significant ($p \leq 0.05$) hypoglycemic effects in alloxan-induced as well as STZ-induced diabetic rats when compared with the control group and standard drug. Although human studies found that using *M. koenigii* leaves juice or powder has shown a significant decrease the blood glucose in diabetic patients, the study population, period of study and evaluation methods, and others are not enough to decide the conclusion. The longitudinal studies should be carried out to make a final decision.

CONCLUSION

This present review confers the 'anti-hyperglycemic effect of the *M. koenigii* as capable herbal material in managing diabetes mellitus due to its availability, efficacy, and clinical safety based on the literature review, *in vitro*, *in vivo*, and related clinical studies. This review reported the potential of curry leaf and its extract to be a high-value dietary product in terms of its anti-hyperglycemic effects and industrial profits. Therefore, the present review provides a valuable document for the researchers to do the future scientific-related clinical trials in diabetic patients.

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None.

AUTHORS' CONTRIBUTION

Vinotha Sanmugarajah: collected data, conceived and design the analysis, writing of the paper. **Gowri Rajkumar:** contributed data, conceived and design the analysis.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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