Anti –diabetic activity of *Murraya koenigii* – A comprehensive review

ABSTRACT

Diabetes mellitus, one of the noncommunicable illnesses, is a severe problem worldwide as one of the leading causes of death. Because existing synthetic medications have various drawbacks, researchers are still looking for better anti-hyperglycemic treatments. Plants have been used in ancient medicine for thousands of years. India is the biggest producer of medicinal plants and is aptly regarded as the "World's Botanical Garden." *Murraya koenigii Linn*, also known as Meethi neem, is a Rutaceae plant. Curry trees are unique to India and likely found almost everywhere else on the subcontinent, except in the Himalayan highlands. For centuries, curry leaves were used as an antiemetic, diarrhea remedy, febrifuge, and blood purifier. Curry leaves are useful as an antioxidant, anti-diabetic, antibacterial, antihypertensive, cytotoxic, and in treating bronchial respiratory problems. Traditionally, the leaves were utilized as a spice in curries as well as other dishes. It includes coumarins and derivatives, alkaloids, flavonoids, phenolic compounds, and essential oil. Numerous studies have found that these phytochemicals have a significant effect on type 2 diabetes. This review focuses on this plant's anti-diabetic action and concludes that it has the potential to be evaluated as a candidate for developing a new diabetes mellitus medication.

Keywords: Medicinal plants, *Murraya koenigii*, Diabetes mellitus

1.INTRODUCTION

Diabetes mellitus, among the most frequent endocrine and metabolic illnesses, has caused enormous morbidity and death as a result of microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular disease) effects. In human bodies, anti-oxidative processes, both enzymatic and non-enzymatic, contribute to the reduction of reactive oxygen species, which are linked to a number of degenerative disorders, including diabetes [Ponnulakshmi et al., 2019]. The sickness is spreading swiftly over the world and is impacting people in every country. Diabetes patients have elevated blood glucose levels due to insulin insufficiency [Ponnusamy et al., 2011]. Type 2 diabetes, also called the non

diabetic Mellitus, has to be the most common type of diabetes, accounting for 90 percent to 95 percent of instances in which the body fails to make sufficient insulin or use it properly [Li et al., 2004]. According to the World Health Organization, the diabetes population will reach 300 million or more by 2025 [GY et al., 2005]. Insulin and various oral anti-diabetic medications, including sulfonylureas, biguanides, and glinides, are currently available for diabetes treatment. Many of them have a variety of significant side effects; as a result, one of the most critical areas of research is the search for more effective and safer hypoglycemic agents[Saxena et al., 2004].

2. COST OF DIABETES

Numerous research on the cost of sickness have been conducted as a result of the economic burden of diabetes mellitus. Diabetes costs may be divided into three categories: direct costs, indirect costs, and intangible costs[Pagano et al., 1999; Sobocki et al., 2007]. Both direct health care expenditures (diagnostic, treatment, care, and preventive) and direct non-health care costs are included in direct costs (transport, housekeeping, social service and legal cost). With complications, the total direct cost is ₹ 28,888/- per year[American Diabetes Association ,2013]. Absenteeism, lost output, and incapacity are all examples of indirect costs. With complexity, the total indirect cost is 1746/- per annum. [Glynn et al.,2011]. Finally, intangible costs include costs associated with social isolation and dependency, low socioeconomic status, mental health and behavioural disorders, and a reduction in quality of life. [Rodwin et al., 2013].

3.PLANT AS ALTERNATIVE SOURCE

The hypoglycemic impact of various plants used as anti-diabetic agents has been established, and the mechanisms underlying this effect are being researched. This article discusses natural compounds with anti-diabetic characteristics that operate as insulin-mimetic or secretagogues. Traditional remedies derived from commonly available medicinal plants hold considerable promise for developing new anti-diabetic medications [Jung et al., 2006].

Certain medicinal herbs have recently been described to be effective in the treatment of diabetes throughout the world, and they have been used empirically in anti-diabetic and antihyperlipidemic drugs. Plants' anti-hyperglycemic action is mainly related to their capacity to restore pancreatic tissue function by increasing insulin secretion, inhibiting glucose absorption in the intestine, or facilitating metabolites in insulin-dependent activities. Even though literature

lists over 400 plant species with hypoglycemic action, hunting for new anti-diabetic medications from natural plants remains appealing since they contain chemicals that have alternative and harmless effects on diabetes mellitus.

Plant-derived active components that have shown action as in treatment of diabetes include alkaloids, glycosides, galactomannan gun, polysaccharides, peptidoglycans, hypoglycin, guanidine, steroids, sugars, glycopeptides, terpenoids, amino acids, and inorganic ions [Grover et al.,2002].

Curry leaves are *Murraya koenigii (M. koenigii)* (L) Spreng of the Rutaceae family. *M. koenigii* is found all across the world's tropical and subtropical regions. [Wojdyo et al.,2007]. Only two Murraya species, *M. koenigii* and *M. paniculate* are found in India, out of 14 worldwide. *M. koenigii* is more important because of the wide range of traditional therapeutic characteristics it possesses. This plant has been utilized in various ways for millennia and is known as "krishnanimba" in Indian Ayurvedic medicine [Ahluwalia et al., 2004]. *M. koenigii's* leaves, roots, bark, and fruit have been demonstrated to support a range of biological activities. Even after drying, aromatic bioactive components in *M. koenigii* leaves retain their flavor and other properties [Amna et al.,2019]. The leaves of *M. koenigii* have a slightly bitter taste, a pungent odor, and are somewhat acidic. They are used as antihelminthics, analgesics, digestives, and appetizers in Indian cuisine [Desai et al., 2012]. Piles, inflammation, itching, fresh cuts, diarrhea, bruising, and edema are treated using M. Koenig's green leaves. To some extent, the roots are purgative. They are stimulating and are used to treat aches and pains in the body.The bark can be used to treat snakebites [Gajaria et al., 2015]. The essential oil obtained from *M. koenigii* leaves has been proven in animal models to have anti-oxidative and hepatoprotective properties [Ma et al., 2016] antibacterial, antifungal, anti-inflammatory, and nephroprotective effects [Tripathi et al., 2018]. Several chemical elements of distinct carbazole alkaloids and other significant metabolites, such as terpenoids, flavonoids, phenolics, carbohydrates, carotenoids, vitamins, and nicotinic acid, have been attributed to the therapeutic qualities of *M. koenigii* from various regions of the plant.

M. koenigii has received increased interest in traditional medicines and home cures in recent years. On the other hand, few research have been undertaken to assess *M. koenigii's* pharmacological and therapeutic usefulness in improving health and healing sickness[Dar et

al.,2017]. This review aims to present previous and existing major studies on *M. koenigii* activity in diabetics.

4.Traditional and Medicinal Uses of *M. koenigii*

M. koenigii essential oils and fresh leaf powder can be used to season foods and make ready-to-eat meals. The essential oil from leaf extracts can also be employed as a perfume, and taste agent in traditional practise due to its increased antibacterial activity [Erkan et al.,2012]. Fresh curry leaves are cooked with coconut oil until they have been crushed to a black residue to make a great hair tonic for restoring normal hair tone and promoting hair development. Curry leaves have long been used as an antidiarrheal, antifungal, blood purifying, anti-inflammatory, and anti-depressant medication, either whole or in little amounts. [Joshi et al.,2018].

Different plant parts, like the leaves, roots, and bark, could be used as tonics to induce digestion and flatulence or as antiemetics [Adebajo et al.,2006]. The leaves turn unpleasant to the taste after infusion and are useful in lowering fever. The root's juice is used to treat kidney pain [Tembhurne et al., 2009]. The leaves and roots can be used as an antihistamine, analgesic, piles treatment, body heat reducer, and thirst quencher, as well as to relieve inflammation and irritation. They're also suitable for treating leucoderma and blood problems. The green leaves can be consumed raw to treat diarrhea, and the paste made from boiling the leaves in milk can be used to treat toxic bites and eruptions. [Sim et al.,2011].

5.Other uses

Using essential oils Murraya koenigii is utilised in formulations as a sun protection and erythema agent [Prakash et al., 1974]. Curry leaf oil with your usual skin care cream or lotion helps to heal skin problems such as pimples, athlete's foot, ringworm, itches, acne, boils, and septic wounds and burns by applying it to the afflicted region[Dasgupta et al., 2003]. Due to the active constituents -pinene and caryophyllene, essential oils of *Murraya koenigii* were tested for toxicity and repellant action against Callosobruchus maculatus[Jamil et al.,2016]. Murraya koenigii structure-function investigations suggest that the protein has a trypsin inhibitory effect as a compact structure with helical content as temperature rises. In Dalton's Ascitic Lymphoma,

the effects of *Murraya koenigii* column extract demonstrate a protective effect [Gupta et al.2010]. The ability to include dried curry leaf powder into everyday foods boosts micronutrient sources[Harve et al., 2004]. *Murraya koenigii* aqueous extract has larvicidal, pupicidal repellent, and anti-vector activities against larvae and pupae. [Arulselvacn et al., 2007Curry leaf oil's high vitamin A and calcium content is used to treat osteoporosis, calcium shortage, and cancer radiation and chemotherapy treatments [Srinivasan et al., 2005]. *Murrya koenigii* is used to cure or prevent orofacial dyskinesia (OD), which is caused by neuroleptics[Xie et al., 2006]. The anti-Trichomonas gallinae action of carbazole alkaloids derived from *Murrya koenigii* extract and its derivatives [Shree et al., 2007]. Curry leaves and essential oil are used both orally and topically for healthy, long, strong, and glossy hair. A balanced diet with an equal percentage of vitamins, minerals, iron, and other nutrients is needed to keep hair healthy. [Debosree et al.,2012]. Curry leaf oil aids in muscle and tissue contraction. Curry leaf extract aids in the reduction of white areas on the body and helps with pigmentation. Curry leaf fresh leaves, dried leaf powder, and essential oil are commonly used to flavour soups, curries, fish, meat, and egg meals, as well as classic curry powder mixes, seasoning, and ready-to-use other culinary preparations. *Murraya koenigii* essential oil is used in the soap and cosmetic sector for aromatherapy. *Murraya koenigii* is used to treat bruises, eruptions, and deadly animal attacks. [Mittal et al.,2014].

6.Phytochemistry of *M. koenigii*

The leaves, roots and stem bark of *M. koenigii* have been used to isolate a variety of phytochemicals. Alkaloids, flavonoids, terpenoids, and polyphenols have been found in *M. koenigii* extracts of leaves, roots, stem bark, fruits, and seeds. Moisture is 63.2 percent, protein is 8.8%, carbohydrate is 39.4%, total nitrogen is 1.15 percent, fat is 6.15 percent, total sugars are 18.92 percent, starch is 14.6 percent, and crude fiber is 6.8 percent in the plant leaves. Vitamin A (B-carotene): 6.04 0.02 mg/100 g; vitamin B3, (niacin): 2.73 0.02 mg/100 g; vitamin B1 (thiamin): 0.89 0.01 mg/100 g; calcium: 19.73 0.02 mg/100 g; magnesium: 49.06 0.02 mg/100 g; sodium: 16.50 0.21 mg/100 g [Igara et al.,2016] The alcohol-soluble extract has a value of 1.82 percent, ash has a value of 13.06 percent, acid-insoluble ash has a value of 1.35 percent, cold water (20 °C) extractive has a value of 27.33 percent, and maximum of hot-water-soluble extractive has a value of 33.45 percent. Carbazole alkaloids, essential oils, terpenoids, and

flavonoids all play important functions in the human body. List of main phytocompounds present in *M. koenigii* was listed in Table 1

7.Antidiabetic Activity of *M. koenigii*

Because of their low cost, medicinal plants are particularly useful in managing diabetes mellitus in developing countries. Diabetes mellitus, a metabolic disorder, is rapidly being a major public health concern. In recent years, numerous phytochemicals with anti-diabetic properties have been found in plants. *M. koenigii* leaf alkaloids were examined and found to inhibit the aldose reductase enzyme, glucose consumption, and other enzyme systems, potentially extending anti-diabetic benefits[Patel et al., 2012]. The -glucosidase inhibitory property of *M. koenigii* was examined, and it was discovered to inhibit glycosidase. Patients with type 2 diabetes are commonly treated with alpha-glucosidase inhibitors [Gul et al., 2012]. According to one study, an ethanolic extract of *M. koenigii* reduced blood glucose levels significantly, and this action of M. koenigii reducing blood glucose is mediated by antioxidant properties and insulin-mimetic effects. *M. koenigii* also demonstrated a high antioxidant effect, lowering MDA levels, increasing GSH levels, and significantly lowering the homeostatic model assessment (HOMA)-insulin resistance index. Overall, *M. koenigii* appears to have anti-diabetic and antioxidant properties in rats. [Husna et al.,2018].

8.Hypoglycemic activity:

Feeding the leaves to rats resulted in hypoglycemia because it enhanced hepatic glycogenesis, as evidenced by increased glycogen synthetase activity. The activity of glycogen phosphorylase and gluconeogenic enzymes reduced, indicating a reduction in glycogenolysis and gluconeogenesis. [Fiebig et al.,1985].

The hypoglycemic effect can be achieved by increasing insulin production from [beta]-cells of Langerhans islets in the pancreas or emancipating insulin from its bound state [Gautam et al., 2012]. The antioxidant defence system of plasma and pancreas, as well as the probable protective impact of *M. koenigii* leaf extract against -cell damage, were examined in streptozotocin-induced diabetic rats. It was determined that *M. koenigii* therapy protects against diabetes by lowering oxidative stress and pancreatic-cell damage.

The effects of *M. koenigii* leaves were researched by Arulselven and Subramanian. Streptozotocin-induced diabetic rats were used in the experiment, and they were given 200 mg [kg.sup.-1] *M. koenigii* leaves for 30 days. *M. koenigii* dramatically reduced blood glucose and glycosylated hemoglobin levels while significantly increasing insulin and liver glycogen levels, according to the findings. It also decreased lactate dehydrogenase, glucose-6-phosphatase, fructose-1,6-diphosphatase, and glycogen phosphorylase activities while increasing hexokinase and pyruvate kinase activities. The effects of *M. koenigii* fruit juice were researched by Tembhurne and Sakarkar [Tembhurne et al.,2009]. They used alloxan-induced diabetic mice treated for 15 days with 2.5 and 5.0 ml/kg *M. koenigii* fruit juice...

The hypoglycaemic effect of *M koenigii* leaf extracts, as well as the number of spices employed, was investigated, proving that they can be utilized as an effective anti-diabetic diet [Srinivasan et al.,2015].

M. koenigii leaf extract reduced blood glucose levels by 13.1, 16.3, and 21.4 percent and 3.2, 5.58, and 8.21 percent for mild and moderate diabetes produced by alloxan in rats fed the extract as a meal, demonstrating its potential as an antihyperglycaemic agent[Yadav et al., 2004].

The effect of an aqueous extract of *M. koenigii* leaves on hypoglycaemic activity in normal and alloxan-induced diabetic rabbits was compared to the impact of a common hypoglycemic medication, tolbutamide. In both normal and diabetic rats, a single treatment of varied dose levels (200, 300, and 400 mg/kg) of the aqueous extract resulted in a reduction in blood glucose levels [Kesari et al., 2005].

Curry leaf extract has been shown to lower blood cholesterol and blood glucose levels in diabetic rats, as well as reduce body weight after therapy [Xie et al.2006].

For 30 days, oral administration of an ethanolic extract of *M. koenigii* to Streptozotocin-induced diabetic rats dramatically reduced blood glucose, glycosylated hemoglobin, urea, uric acid, and creatinine levels in the diabetic treatment group of animals[Aruselvan et al.,2006].

For a brief period of 6 hours, the aqueous extract of *M. koenigii* had a favorable effect in reducing the severity of diabetes in alloxan and normal induced diabetic rabbits48.

M. koenigii considerably reduced blood glucose levels, according to the findings. Many types of research [Harve et al.,2004] examined flavonoids, quercin, metformin, quinolizidine, anthocyanin, catechin, flavone, phenylpropanoids, lipoic acid, and coumarin as the most phytochemical compounds having anti-diabetes activity.

Traditional or alternative therapy, in addition to mainstream pharmaceuticals, plays a crucial part in the treatment of diabetes mellitus. It must understand how to use it and what phytochemical ingredients are present. The goal of this review study was to compile the new medicinal plant, *M. paniculata*, as the therapy of choice. All of this data will aid researchers in their investigation of the scientific evidence.

Alkaloids found in the leaves of *M. koenigii* have been studied and shown to inhibit the aldose reductase enzyme, glucose consumption, and other enzyme systems, potentially prolonging antidiabetic effects[Patel, et al.,2012]. *M. koenigii* was investigated for its ability to inhibit glycosidase, and it was discovered to do so. Alphaglucosidase inhibitors are commonly used to treat type 2 diabetic patients. [Gul et al., 2012]. An ethanolic extract of *M. koenigii* exhibited a considerable reduction in blood glucose levels, according to one research, and this action of M. koenigii decreasing blood glucose is mediated by antioxidant qualities and insulin mimetic effects. Furthermore, *M. koenigii* had a strong antioxidant impact, lowering malondialdehyde (MDA), boosting GSH, and dramatically lowering the homeostatic model assessment (HOMA) insulin resistance score. Overall, *M. koenigii* appears to have anti-diabetic and antioxidant properties in rats. [Husna, et al., 2012].

9. ADVANTAGES OF M. Koenigii

The best health advantages of Curry Leaves are listed here.

- • Curry Leaves Aid in Cholesterol Reduction
- Curry Leaves Aids Digestion
- Curry Leaves Benefits the Liver
- Curry Leaves Promotes Hair Growth
- Curry Leaves Improves Eye Health
- Curry Leaves Eradicates Bacteria

- Curry Leaves Promotes Weight Loss
- Curry Leaves Prevents Anemia

Disadvantages of M. koenigii

Although no harm has been recorded from curry leaves, it may be detrimental in some instances or at excessive quantities.

• Some individuals may experience allergic reactions. Its usage should be ceased in such a case.

• Pregnant and breastfeeding women should see a doctor before using it, as some of its negative effects are common in this condition.

• At the same time, in some situations, the use of its oil can weaken the hair roots and cause them to fall out.

10.Conclusions

The present review discusses *M. koenigii's* medicinal uses, phytochemical constituents, and pharmacological qualities, with a focus on its anti-diabetic properties. *M. koenigii* contains alkaloids, polyphenols, terpenoids, and flavonoids, among other bioactive substances. M. koenigii and its substances appear to have anticarcinogenic, proapoptotic, antiangiogenic, antimetastatic, immunomodulatory, and antioxidant properties. The broad activity of *M. koenigii* and its derivatives in cell signalling pathways at multiple levels in various illnesses illustrates the molecular processes behind these activities. *M. koenigii* and its derivatives reduce oxidative stress, neurotoxicity, neuroinflammation, neuronal loss, and cognitive dysfunctions. However, like other polyphenols, *M. koenigii's* actions are restricted to some extent by its bioavailability, and in such cases, increased efficiency should be pursued. As a result, future research should involve additional experimental studies on improving bioavailability and efficiency in clinical trials.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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Table 1. The pharmacological activity of *M. koenigii's* key bioactive substances

S.No	Compound Name	Activity
1	Mahanine	Cytotoxicity, anti- microbial, and anti- cancer
2	Mahanimbine	Cytotoxicity, anti- oxidant, anti- microbial, anti- diabetic, and hyperlipidemic
3	Isomahanine	Cytotoxicity, anti- oxidant, anti- microbial, anti- diabetic, and hyperlipidemic
4	koenimbine	Cytotoxicity and anti- diarrhea
5	Girinimbine	Anti- tumor
6	Isolongifolene	Anti- oxidant and neuroprotective
7	Pyrayafoline D	Anti- cancer and anti- bacterial
8	Murrayafoline	Cytotoxicity and anti- inflammatory
9	Murrayazoline	Cytotoxicity and anti- tumor
10	Koenoline	Cytotoxicity
11	9- formyl- 3- methyl carbazole	Anti- oxidant
12	O- Methylmurrayamine	Anti- oxidant and neuroprotective
13	Koenine	Anti- oxidant
14	Koenigine	Anti- oxidant
15	Mukonicine	Anti- oxidant
16	Mahanimbinine	Anti- oxidant, anti- microbial, anti- diabetic, and hyperlipidemic
17	Murrayacinine	Anti- oxidant, anti- microbial, anti- diabetic, and hyperlipidemic
18	Mahanimboline	Cytotoxicity, anti- oxidant, anti- microbial, anti- diabetic, and hyperlipidemic
19	Mukoeic acid	Anti- oxidant
20	Murrayanine	Anti- oxidant