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"Exploring the Anti-Diabetic Potential of *Limonia acidissima*: A Comprehensive Review of In-Vivo Studies and Therapeutic Insights"

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Abstract:

Diabetes mellitus is a type of chronic metabolic disorder categorized by insufficiency in insulin activity and/or insulin secretion with multiple etiologies, defined by problems in the metabolism of proteins, lipids, and carbohydrates as well as consistently elevated blood sugar levels. With a variety of treatment options, most people with type 2 diabetes still struggle to reach their glycaemic targets, and their disease gets worse if left untreated. Current euglycemia treatments frequently have negative side effects. However, traditional medicinal herbs have strong antidiabetic properties, improving metabolic pathways without having negative side effects. Wood apple, or "kaitha," is another name for Limonia acidissima, one of the numerous easily accessible therapeutic herbs. According to preliminary , L. acidissima fruit ethanolic extract may have antidiabetic effects. The goal of this study was to determine the methanolic extract of Limonia acidissima (MELA) leaves' graded-dose antidiabetic activity in rats. Methods and Materials: Eight male Wistar rats were randomly assigned to one of six groups: normal control, diabetic control (alloxan-induced), or test groups, in which different dosages of MELA (100 mg/kg, 200 mg/kg, and 400 mg/kg) or Metformin (100 mg/kg) were given after alloxan induction. Throughout the course of 28 days, random blood sugar (RBS) levels were assessed at predetermined intervals. Conclusion: The results of our study indicated that MELA had strong, dose-dependent antidiabetic effects.

keywords: Diabetes mellitus, Limonia acidissima, medicinal herbs, methanolic extract, experimental studies.

Introduction

Overview:

Diabetes mellitus (DM), a serious metabolic disease, affects a large number of people. Experts estimate that by 2045, the number of affected individuals would increase to 12.2% (783 million), up from the current 10.5% (537 million)[1]According to the IDF Diabetes Atlas, 382 million individuals worldwide are estimated to have diabetes. The number will rise to 592 million, or one in ten, by 2035. Furthermore, 316 million individuals already have a high risk of type 2 diabetes, and that figure is predicted to increase to 500 million[2].

Diabetes is a metabolic disease with several etiologies that is typified by persistently high blood sugar levels and abnormalities in the metabolism of proteins, fats, and carbohydrates [2]. Despite the fact that type 2 diabetes has several treatment choices, the majority of patients still have difficulty meeting their glycaemic goals, and their condition worsens unchecked. Numerous micro- and macrovascular problems brought on by uncontrolled diabetes increase morbidity, mortality, and healthcare expenses. Furthermore, there are a number of negative effects linked to the existing treatments for euglycemia. Nonetheless, there is proof that traditional medicinal herbs provide significant anti-diabetic benefits without any negative side effects in addition to affecting metabolic pathways [1], [3].

Of the 21,000 medicinal plants listed by the World Health Organization (WHO), 2500 species are found in India. Eight hundred of these 2500 plants have been shown to possess antidiabetic qualities[1]. *Limonia acidissima*, also referred to as wood apple or "kaitha," is one of the many readily available medicinal herbs. Throughout Southeast Asia, including India, the genus *Limonia* is widespread. It contains the somewhat big deciduous tree *Limonia acidissima Linn*, also known as *Feronia limonia* (Family: Rutaceae, subfamily: Aurantioideae). *L. acidissima* has been shown to have anti-bacterial, hepatoprotective, diuretic, antidiabetic, wound-healing, antinociceptive, and anti-cancer qualities in all of its components. Early experimental research has indicated that the ethanolic extract of *L. acidissima* fruits may have antidiabetic properties[1] The fruit can treat blood pressure, diarrhea, ulcers, diabetes, and cancer. Frequent ingestion of this fruit aids in disease prevention[4].

Diabetes mellitus:

Diabetes mellitus is a type of chronic metabolic disorder categorized by insufficiency in insulin activity and/or insulin secretion. Anomalies in proteins, carbohydrates and lipids metabolism can arise due to the lack of insulin, an anabolic hormone[5] Low insulin levels, insulin resistance of target tissues, insulin receptor levels, mainly in skeletal muscles and adipose tissue, and to a lesser extent in the liver, signal transduction system, effector enzymes, genes, and/or signal transduction pathway are the causes of these metabolic abnormalities[5] Exocrine gland producing digestive enzymes, such as trypsin and chymotrypsin[2] .

There are four different kinds of hormone-secreting cells in the islets of Langerhans. These are the Glucagon is secreted by alpha cells, insulin by beta cells, gastrin by delta cells, and pancreatic polypeptide by F cells. These cells are not dispersed at random within an islet; beta Alpha, delta, and F cells encircle the cells that make up the islet's center. The hormone insulin is a polypeptide. The production of insulin occurs in the beta cells and is kept in the pancreas as granules[2].

Types of Diabetes Mellitus

TYPE 1 Diabetes

It results from the body's failure to produce insulin and also referred to as insulin-dependent diabetes mellitus, IDDM for short, and juvenile diabetes.
Type 1 Pathophysiology

The metabolic abnormalities linked to IDDM are caused by a lack of insulin secretion brought on by the autoimmune death of pancreatic β-cells. Furthermore, patients with IDDM have aberrant pancreatic α-cell activity, which encourages excessive glucagon secretion. Glucagon production is normally decreased in response to hyperglycemia; however, in patients with IDDM, hyperglycemia does not inhibit glucagon secretion. The resulting unnecessarily high glucagon levels exacerbate the metabolic abnormalities caused by insulin insufficiency[2] .

Type 2 Diabetes

Type 2 diabetes occurs when the islets of Langerhans produce and secrete less insulin, or when insulin resistance occurs despite an excess of insulin being available.

Due to its gradual onset, the disease may not be identified in its early stages. Insulin resistance, which eventually leads to type 2 diabetes, is most frequently caused by obesity and inactivity[2]

Regulation of Blood Glucose :

Insulin and glucagon are released to control blood glucose levels, which is based on a negative feedback loop. The pancreatic islet of Langerhans' B cells secrete insulin, a 51-amino acid polypeptide made up of two chains (A and B) joined by disulphide bridges, in response to elevated blood glucose levels. Pro-hormone convertases (PC I and PC 2) and exo-protease carboxypeptidase synthesize insulin from pro-insulin. These enzymes' activity produces C-peptide and insulin[6].The tyrosine kinase insulin receptor, which is composed of two extracellular

(a) and two intramembrane (b) subunits connected by disulfide links, is where insulin binds. The beta subunit of the tyrosine kinase insulin receptor is auto phosphorylated when insulin binds to it. Insulin instructs the liver to store the extra glucose as glycogen. It also causes the body's skeletal and adipose muscle cells to absorb more glucose by causing the glucose transporter (GLUT4) to move to the cell surface. This aids in returning the levels of glucose in the blood to normal[6] When the glucose concentration in the blood is low , the a cells of the pancreas are stimulated to release glucagon. Glucagon signals the liver to convert stored glycogen into glucose which is released into the blood to achieve homeostasis.

Table 1 : Diagnostic tect of Diabetics mellitus in tabular form[7]

Diagnostic Test	Description
Urine Glucose (Excretory Product Sugar)	Detection of glucose in urine may indicate elevated blood glucose levels. However, it is not a definitive test for diabetes as it is influenced by renal threshold.
Blood Glucose Levels	Measurement of fasting or random blood glucose levels. A single abnormal result should not be used alone for diagnosis.
Oral Glucose Tolerance Test (OGTT)	Involves measuring blood glucose levels at intervals after consuming a glucose-rich drink to assess how the body handles glucose.
Glucose Tolerance Test (GTT)	Assesses how quickly glucose is cleared from the blood over a set period after ingestion. A diminished tolerance indicates diabetes.
Renal Threshold for Glucose	Evaluates the glucose level at which kidneys begin to excrete glucose into urine. Lower thresholds can indicate diabetes.
Diminished Glucose Tolerance	Impaired ability of the body to metabolize glucose, suggesting prediabetes or diabetes.
Increased Glucose Tolerance	A rare finding; usually associated with other metabolic disorders, not typical in diabetes.
Renal Glycosuria	Presence of glucose in urine without elevated blood glucose levels, usually due to a low renal threshold.
Extended Glucose Tolerance Curve	Monitoring blood glucose over a longer period after a glucose load to assess sustained tolerance.
Cortisone-Stressed Glucose Tolerance Test	Tests how blood glucose levels respond to cortisone, which can reveal latent diabetes.
Intravenous Glucose Tolerance Test (IVGTT)	Involves injecting glucose directly into the bloodstream to evaluate the body's glucose processing efficiency.

Insulin and oral hypoglycemic medications for treatment:

Since nature is so effective at reducing postprandial hyperglycemia and avoiding hypoglycemia in between meals, insulin therapy should try to emulate it. Insulin injections can be administered intramuscularly or intravenously, and the site of administration is equally crucial for improved and safe action of insulin. There are various forms of insulin available, including human, cow, and hog insulin. Insulin treatment is not without its problems and side effects. The most significant side effects are weight gain and hypoglycemia when an insulin dosage is not appropriate and when meals and insulin injections are not timed correctly[8].Biguanides like metformin and

phenformin and sulphonyl urease like glibenclamide and glipizide are oral hypoglycemics that induce hypoglycemia by inducing the release of insulin from pancreatic ß-cells. Metformin is one example of a biguanide that is antihyperglycemic rather than hypoglycemic. Even in high dosages, it does not result in hypoglycemia or the release of insulin from the pancreas. When administered orally rather than intravenously, it has been demonstrated to enhance peripheral glucose uptake and decrease hepatic glucose production by roughly 20–30%. Another theory of action is impaired intestinal absorption of glucose[8].

Table 2 : conventional treatment for hyperglycemia[8]

Drug Class	Examples	Side Effects
Sulfonylureas	Tolbutamide (1st gen), Glyburide (2nd gen)	Associated with weight gain due to hyperinsulinemia.
Biguanides	Metformin (e.g., Glucovance)	Reduces plasma glucose via inhibition of hepatic glucose production, increases muscle glucose uptake, and decreases triglyceride & LDL cholesterol levels.
Alpha-Glucosidase Inhibitors	Acarbose (e.g., Precose)	Major side effects include gas, bloating, and diarrhea.
Thiazolidinediones	Troglitazone, Rosiglitazone (e.g., Avandia), Pioglitazone	Side effects include weight gain and an increase in LDL cholesterol levels.
Meglitinides	Repaglinide (e.g., Prandin)	Common side effects include weight gain, gastrointestinal disturbances, and hypoglycemia.

Herbal drug treatment of diabetes:

As traditional medicine research has advanced over the past few decades, plant-based medications that are eco-friendly, bio-friendly, affordable, and generally safe have emerged from the fringe to the mainstream. The World Health Organization has classified 21,000 plants that are used medicinally worldwide. India is home to 2500 species, 150 of which are employed extensively for economic purposes. Known as the world's botanical garden, India is the world's largest producer of medicinal plants[9]Plant or h It has been revealed that about 800 plants possess antidiabetic properties [10]Herbal products are high in terpenoids, coumarins, phenolic compounds, and other components that lower blood glucose levels. According to ethnobotanical data, there are roughly 1000 plants that may have antidiabetic properties[9] A total of 343 plants worldwide have been examined for their ability to reduce blood glucose levels in lab tests[11].

INTRODUCTION OF *Limonia acidissmia*:

There are several Indian-origin plants that are neglected despite their immense therapeutic significance in treating a number of human ailments. One such plant is the wood apple, which is an edible fruit. In Ayurvedic medicine, fruits, seeds, leaves, roots, and bark are widely utilized to treat peptic ulcers, chronic diarrhea, dysentery, and a variety of other conditions as a laxative and for illnesses.

figure 1: *Limonia acidissima*

Feronia limonia, another name for wood apples, is a member of the Rutaceae family. It India's dry and semi-arid regions are home to the hardiest fruits. Wood apple unripe fruits are acidic in While ripe fruits provide a pleasing flavor, nature[12]. Wood apple fruit was once considered a "poor man's food" in India before processing methods were created in the middle of the 1950s. The tree is given the genus Feronia in honor of the Roman woodland goddess.Along with Elephant is another name for wood apple. Elephants like apples and monkey fruit. Some common names for wood apples are "curd apple," "golden apple," "stone apple," as well for example; these names usually rely on Language, place, and culture [13]

Synonyms[13]

Feronia elephantum Correa,

Feronia limonia (L.) Swingle,

Schinus limonia L.

Vernacular names[13]

Wood Apple, Elephant Apple, Monkey Fruit or Curd Fruit, Kaitha, Kath Bel, Kothu.

Table 3: medicinal uses and bioactive properties of different parts of the Wood Apple (Limonia acidissima): [13]

Plant Part	Medicinal Uses & Properties
Roots	- Treats dyspepsia, diarrhea, and dysentery.
Stem & Root Bark	- Aqueous preparations applied topically for eczema, urticaria, malaria, fever, and jaundice.
Fruit Extract	- Used to alleviate ear conditions (e.g., earaches).

	- Reduces lipid profiles and hepatic glucose-6-phosphatase levels.
	- Increases hepatic glycogen, hexokinase, and HDL cholesterol.
	- Inhibitory effects against **C. albicans, A. tumefaciens, B. subtilis, P. fluorescens**, and **E. coli**.
	- Shows anti-cancer properties.
	- Exhibits anti-amoebic and hypoglycemic activities.
Fruit Pulp	- Used in the treatment of diarrhea and dysentery.
Seeds	- Contains Luvangetin and pyranocoumarin with anti-ulcer properties.
Leaves	- Possesses antifungal properties due to essential oil.
	- Leaves have an anise-like scent and are used as cattle feed.
Bioactive Compounds	- Rich in alkaloids such as **Aegline, Marmesin, Marmin, and Marmelosin (Imperatorin)** with anticancer, antibacterial, and anti-inflammatory activities.
Essential Oils	- Exhibits resistance to microbes responsible for human diseases.

BOTONICAL DESCRIPTION OF WOOD APPLE :

Figure 1: fruit of wood apple tree

Table 4: taxonomical classification of wood apple [12]

Category	Classification
Kingdom	Plantae
Sub-Kingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Sapindales
Family	Rutaceae
Genus	Limonia
Species	L. acidissima

Origin or distribution:

The tree is indigenous to India, but it is also grown in Bangladesh, Pakistan, and Sri Lanka[14] The wood apple originated in South India and Sri Lanka[13] It is primarily found in the Western Himalaya, West Bengal, Chhattisgarh, Maharashtra, Madhya Pradesh, and Uttar Pradesh in India[15] This plant is typically grown in India's central and southern dry forests. The wood apple plant is typically found in forests and propagated as a border plant. Additionally, it is grown in southern America, northern Malaysia, and temperate and tropical Asia[12] . As in the western Himalayas, the tree may reach a height of 450 meters. The tree can withstand drought and thrives in light soils[14]

Morphology:

Plants of the genus *Limonia acidissima* arch in the direction of the neighboring crowning point, where they split into thin branchlets and become enervated at the tips[12]

Limonia acidissima L. is a large tree that can grow up to nine meters (30 feet) tall and has rough, spiky bark[16] Some of the zigzag twigs have axillary spines that are small, straight, and 2–5 cm long. Each of the five to seven pinnate leaflets, which are 25 to 35 mm long and 10 to 20 mm wide, has a citrusy aroma when crushed. 2–3 pairs of opposing leaflets, plus a terminal leaflet[17] The leaves are dark green, alternating, deciduous, and three to five inches long. They have oil glands and, when crushed, they have a faint lemon aroma. Flowers are often tiny, bisexual, abundant, and either dull red or greenish yellow in color[12] Fruit The berry, which has a diameter of 5 to 9 cm, can be either sweet or sour. It is greyish-white in color and 6 mm thick. The berry is a globose, whitish-brown fruit with a diameter of 5-7.6 cm, a robust, woody skin, and many seeds[16] .The woody's strong outer shell is known as its rind. The rind is greyish-white and 6 mm thick.The pulp is sticky, dark, mealy, aromatic, resinous, astringent, sour, or sweet, and it contains a large number of tiny white seeds.The longitudinal bark of deciduous trees up to twenty meters tall is dark grey or black and widely divided. polygamous, 1.3 cm in diameter, dull red flowers in axillary cymes; The calyx is small, flat, five-toothed, pubescent-free, and deciduous; the petals flow freely; When stamens 10–12 are inserted around the disc, the filaments below enlarge, and the face and edges are villous; thick, annular, and pubescent disc, linear-oblong anthers, and a pistillode that is short, and the ovary is superior, having an oblong, fusiform stigma and several ovules[16]

Nutritional Values:

Approximately one-third of the entire fruit is made up of wood apple pulp. Three to five percent of fresh pulp is pectin. The approximate pulp contents per 100g edible portion are: 74g of water, protein 8g, 1.5g fat, 7.5g carbs, and 5g ash. Each 100g edible piece of the seeds contains: water. 4g, 26g of protein, 27g of fat, 35g of carbs, and 5g of ash. 15% citric acid is present in the dried pulp.acid and trace amounts of iron, calcium, and potassium salts[17]

Ayurvedic Medicines Containing Kapitta Elephant Apple:[18]

Vajra Kapat rasa- For treatment of diarrhea and malabsorption syndrome

Nyagrodhadi choorna-In urinary obstruction,dysuria, urinary disorder, diabetes

Dashamoolarishta- Used in anemia, after delivery care of mother, cold, cough, digestive disorder

Active constituents in *L. acidissima* :

Plant Part	Constituents
Leaves	Polyphenols, Flavonoids (Imperatorin, Bergapten, Xanthotoxin), Alkaloids, Steroids (Stigmasterol), Amino Compounds, Psoralen, Orientin, Vitexin, Saponarin, Tannins, Essential Oil
Bark	Marmesin, Feronolide, Feronone
Seeds	Fixed Oil, Carbohydrates, Proteins, Amino Acids, Psoralen, Bergapten, Orientin, Vitexin, Saponarin
Roots	Feronia Lactone, Geranylum Belliferone, Bergapten, Osthol, Isopimpinellin, Marmesin, Marmin
Unripe Fruits	Stigmasterol
Fruit Pulp	Citric Acid, Other Fruit Acids, Mucilage, Minerals

Table 5: active constituents of each part of wood apple[14]

Above given are the phytochemically active components of L. acidissima having antidiabetic, antioxidant,anti cancer and many more medicinal properties.

The presence of alkaloids, terpenoids, phenols, flavonoids, saponins, steroids, glycosides, lipids, mucilage, fixed oils, and gums was shown by the primary phytochemical examination of various plant components of Limonia acidissima L[17]

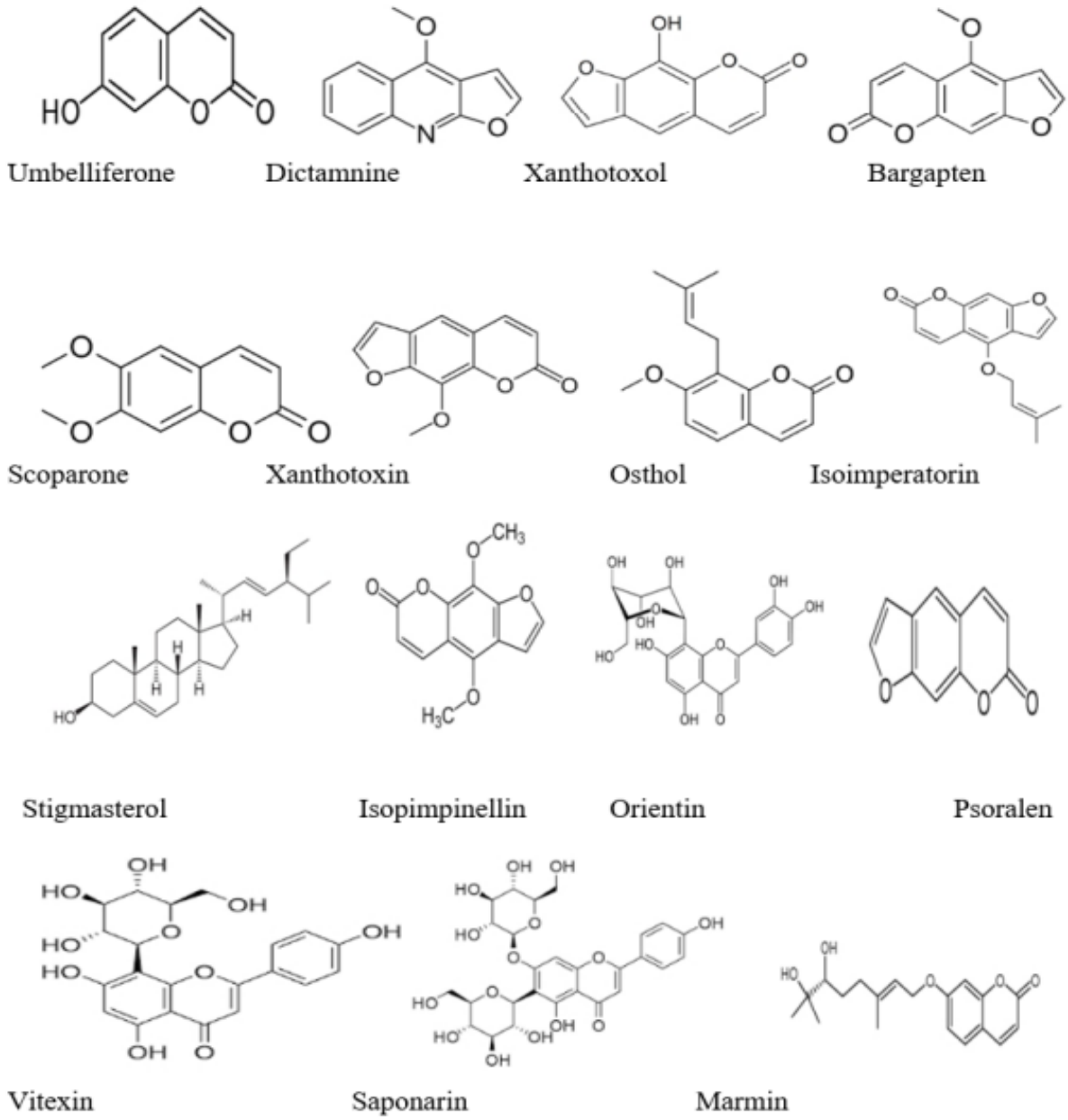


Figure 1 : Some key phytoconstituents in *L.acidissima linn*[16]

In-vivo study of antidiabetic activity:

The goal of this study was to determine the antidiabetic effects of a methanolic extract of Limonia acidissima (MELA) leaves at several doses in rats.

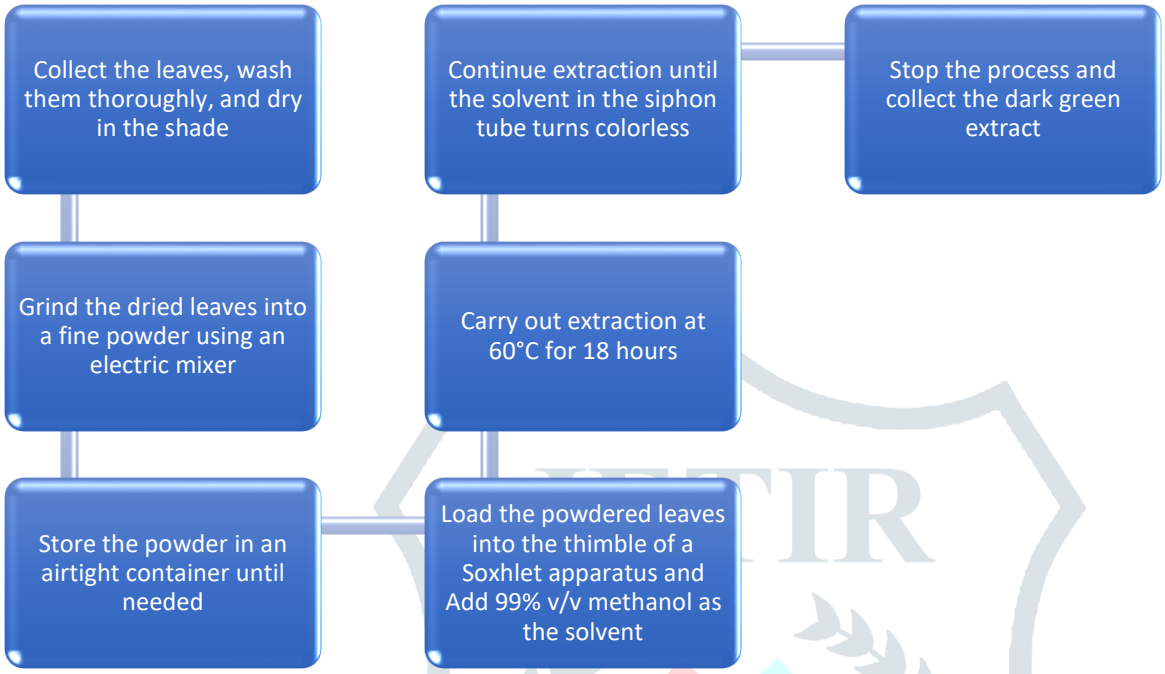
Materials and Procedures:

Male Wistar rats (n=8) were randomly assigned to one of six groups: normal control, diabetic control (alloxan-induced), or test groups, which received different dosages of either metformin (100 mg/kg) or MELA (100 mg/kg, 200 mg/kg, and 400 mg/kg) after alloxan induction. Over the course of 28 days, random blood sugar (RBS) levels were assessed at predetermined intervals[1]

Drugs :

Alloxan monohydrate (S D Fine-Chem Limited, Mumbai), Methanol 99% v/v (Merck), Tablet Metformin 500mg (USV Private Limited, Mumbai).

Preparation of methanolic extract of L.acidissima leaves[1]



MOA:

MELA may have an antihyperglycemic effect in rats with alloxan-induced diabetes through a combination of extrapancreatic and pancreatic pathways. Among these mechanisms could be:

1) Potentiation of Pancreatic Insulin Secretion: intact beta cells in the islets of Langerhans may secrete more insulin when MELA is present. This might make more insulin available, which would aid in better blood glucose regulation.

2) The Mechanisms of Extrapancreas: Mitigation of Glycogenolysis: Like metformin, MELA can reduce the liver's breakdown of glycogen into glucose, called glycogenolysis. Because less glucose would be released into the system, blood glucose levels would drop.

3) Enhanced Glycogenesis: The liver's process of turning glucose into glycogen may be enhanced by the phytochemical components found in MELA leaves, such as alkaloids and saponins. By doing this, more glucose would be stored and kept from entering the bloodstream.

4) Enhanced Glucose Transport: MELA may facilitate the transport of blood glucose to peripheral tissues, such as muscle cells and adipose tissue. This may improve the body's use of glucose and help lower hyperglycemia.

5) Direct Impact on Islet Regeneration or Repair: According to histopathological research, MELA may directly impact the pancreatic islets of Langerhans' ability to regenerate or repair. This is evident by the restoration of the architecture of these islets.

Experiment model:

Young, healthy male albino rats of wistar strain, weighing 150- 250grams, were used and were kept under standard laboratory conditions in a well-ventilated animal house in clean polyvinyl wired cages maintained at 25-26°C temperature and relative humidity 50-70% with a constant 12-hour light/dark schedule. The rats were fed with standard rat pellet chow and clean tap water was made available ad libitum. All the animal procedures were performed after approval from the Institutional Animal Ethics Committee (IAEC) of Mahatma Gandhi institute of medical sciences (MGIMS), Sevagram.

Experiment group[19]

Group	Description	Treatment
Group I	Normal Control (Normal rats)	- Received normal saline (2 mL/kg body weight, IP) only once.
		- Received distilled water (10 mL/kg body weight, orally, once a day for 28 days).
Group II	Diabetic Control (Diabetic rats)	- Treated with alloxan monohydrate (150 mg/kg body weight, IP) only once.
		- No further treatment.
Group III	Test Group 1 (Diabetic rats)	- Treated with alloxan monohydrate (150 mg/kg body weight, IP) only once.
		- Received MELA (100 mg/kg body weight, orally, once a day for 28 days).
Group IV	Test Group 2 (Diabetic rats)	- Treated with alloxan monohydrate (150 mg/kg body weight, IP) only once.
		- Received MELA (200 mg/kg body weight, orally, once a day for 28 days).
Group V	Test Group 3 (Diabetic rats)	- Treated with alloxan monohydrate (150 mg/kg body weight, IP) only once.
		- Received MELA (400 mg/kg body weight, orally, once a day for 28 days).
Group VI	Standard Control (Diabetic rats)	- Treated with alloxan monohydrate (150 mg/kg body weight, IP) only once.
		- Received Metformin (100 mg/kg body weight, orally, once a day for 28 days).

Table 6: experiment group information [19]

Results :

Random blood sugar :

In Group I, administration of DW (PO) did not result in a significant change in the mean RBS levels (p-value=0.341) at any of the time intervals evaluated. While, in Group II, administration of DW (PO), resulted in a statistically significant decrease in the mean RBS levels (p-value=0.001). Similarly, in Group III, IV, V, and VI administration of MELA 100, 200, 400, and Metformin 100 resulted in a statistically significant decrease in the mean RBS levels (all p-values<0.0001)

Results of histopathology:

The islet cells in Group I, which was made up of normal rats, appeared regular and normal. Group II saw atrophy and destruction of the islet of Langerhans' β-cells along with moderate inflammation. Group III's results were comparable to those of Group II, with the exception that there were no inflammatory symptoms and a significant drop in the number of islets of Langerhans. Group IV showed sporadic islet cells as well as an increase in islet density and volume that suggested regeneration. Pancreatic islet cell regeneration or repair was observed in Group V. After receiving 400 mg/kg of MELA extract, the regeneration of necrotic β-cells was substantially more noticeable than in the group that received 200 mg/kg. Furthermore, compared to the diabetic control group, the pancreas in diabetic rats appeared to have a normal structure. Likewise, Group VI showed that the pancreatic β-cells in the islets had been restored or regenerated. Metformin-treated diabetic rats showed nearly normal pancreatic anatomy when compared to the diabetic control. The effects of metformin (100 mg/kg) and MELA (400 mg/kg) were equivalent.

Acute toxicity:

There were no deaths, negative side effects, or notable behavioral changes in the rats given the graded doses of MELA (100, 200, 400, 800, 1000, and 2000 mg/kg) in six groups of six rats each. Given that the rats were extremely active, it is possible that the LD50 was greater than 2000 mg/kg body weight.

Coclusion:

The study suggests that MELA leaves have the potential to be a natural source of antihyperglycemic agents because they exhibit significant antidiabetic activity at different doses (100, 200, and 400 mg/kg). The specific mechanism behind MELA leaves' antihyperglycemic property is still unidentified but more research is required to fully understand this therapeutic property and pinpoint the primary antihyperglycemic compounds.

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