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Therapeutic Role Of Mangifera Indica In The Management And Prevention Of Diabetic Mellitus Complications.

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Abstract: Diabetes mellitus is a group of physiological dysfunctions characterized by hyper glycemia resulting directly from insulin resistance, inadequate insulin secretion, or excessive glucagon secretion. Type 1 diabetes (T1D) is an autoimmune disorder leading to the destruction of pancreatic beta-cells. Type 2 diabetes (T2D), which is much more common, is primarily a problem of progressively impaired glucose regulation due to a combination of dysfunctional pancreatic beta cells and insulin resistance The chronic metabolic disorder diabetes mellitus is a fast-growing global problem with huge social, health, and economic consequences. It is estimated that in 2010 there were globally 285 millionpeople (approximately 6.4% of the adult population) suffering from this disease. diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. These high blood sugar levels produce the symptoms of repeated urination, increased hunger, and increased thirst. Some of the diabetes patients are asymptomatic, especially those with type 2 diabetes during the early years of the disease. Others with marked hyperglycemia, especially in children with absolute insulin deficiency, may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma, and if not treated death, due to ketoacidosis or rarely from non-ketotic hyperosmolar syndrome. Some of the diabetes patients are asymptomatic, especially those with type 2 diabetes during the early years of the disease. Others with marked hyperglycemia, especially in children with absolute insulin deficiency, may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma, and if not treated death, due to ketoacidosis or rarely from non-ketotic hyperosmolar syndrome

Index Terms – Diabetes Mellitus;complications; Mangifera indica ; leaves extract ; natural compounds

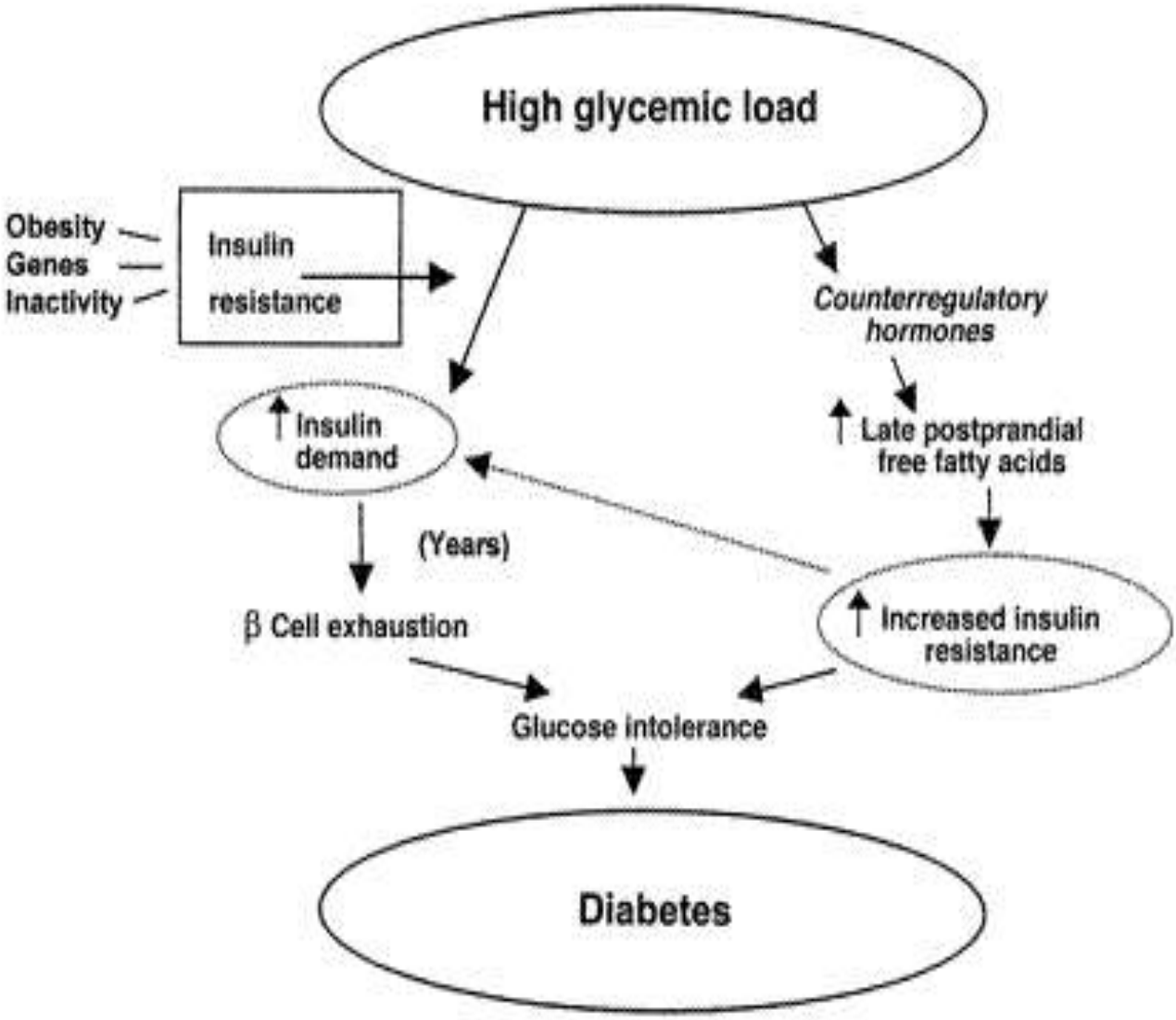
I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose (hyperglycemia) resulting from defects in the body's ability to produce insulin, use insulin, or both. Insulin is a hormone produced by the pancreas that helps glucose enter cells to be used for energy. When insulin action is impaired, glucose accumulates in the bloodstream, leading to short-term symptoms and long-term complications. Types of Diabetes Mellitus 1. Type 1 Diabetes o Caused by autoimmune destruction of pancreatic beta cells. o Leads to absolute insulin deficiency. o Often develops in childhood or adolescence but can occur at any age. o Requires lifelong insulin therapy 2. Type 2 Diabetes o Characterized by insulin resistance and a gradual decline in insulin production. o Most common type (over 90% of cases). o Strongly associated with obesity, sedentary lifestyle, and genetic factors. o Managed with lifestyle changes, oral medications, and sometimes insulin. 3. Gestational Diabetes o Occurs during pregnancy due to hormonal changes causing insulin resistance.

2.Background

- Diabetes mellitus is a common endocrine and metabolic disorder that involves problems with insulin secretion & insulin action leading to the elevated blood glucose level.
- According to the International Diabetes Federation, 529 million people were suffered by diabetes in 2021 with an estimated death about 6.7 million each year.
- In India according to WHO it is 31.7 million in 2000 & it would increased up to 79.4 million by 2030.some drugs used to treat diabetes such as certain oral hypoglycemics can lead to side effects like low blood sugar, lactic acidosis & gastrointestinal disturbance. In addition to this, many herbs have strong anti-diabetic properties.
- It occurs from the combination of modifiable risk factors such as diet and physical exercise & non modifiable risk factors such as age, gender, ethnicity & genetics
- Other predisposing factors are gestational diabetes, use of specific medications, depression, alcohol consumption & smoking.

3.Pathophysiology & Complications



Oxidative stress is thought to be an important factor in the development of type 2 diabetes (T2DM). This happens when the body produces too many reactive oxygen species (ROS)—tiny This damage increases oxidative stress, which then contributes to diabetes and its complications (like problems with blood vessels, eyes, kidneys, and heart). Researchers have found that different body processes and pathways make oxidative stress worse. Because of this, checking oxidative stress biomarkers (chemical signals that show stress levels) might help doctors predict or diagnose type 2 diabetes.

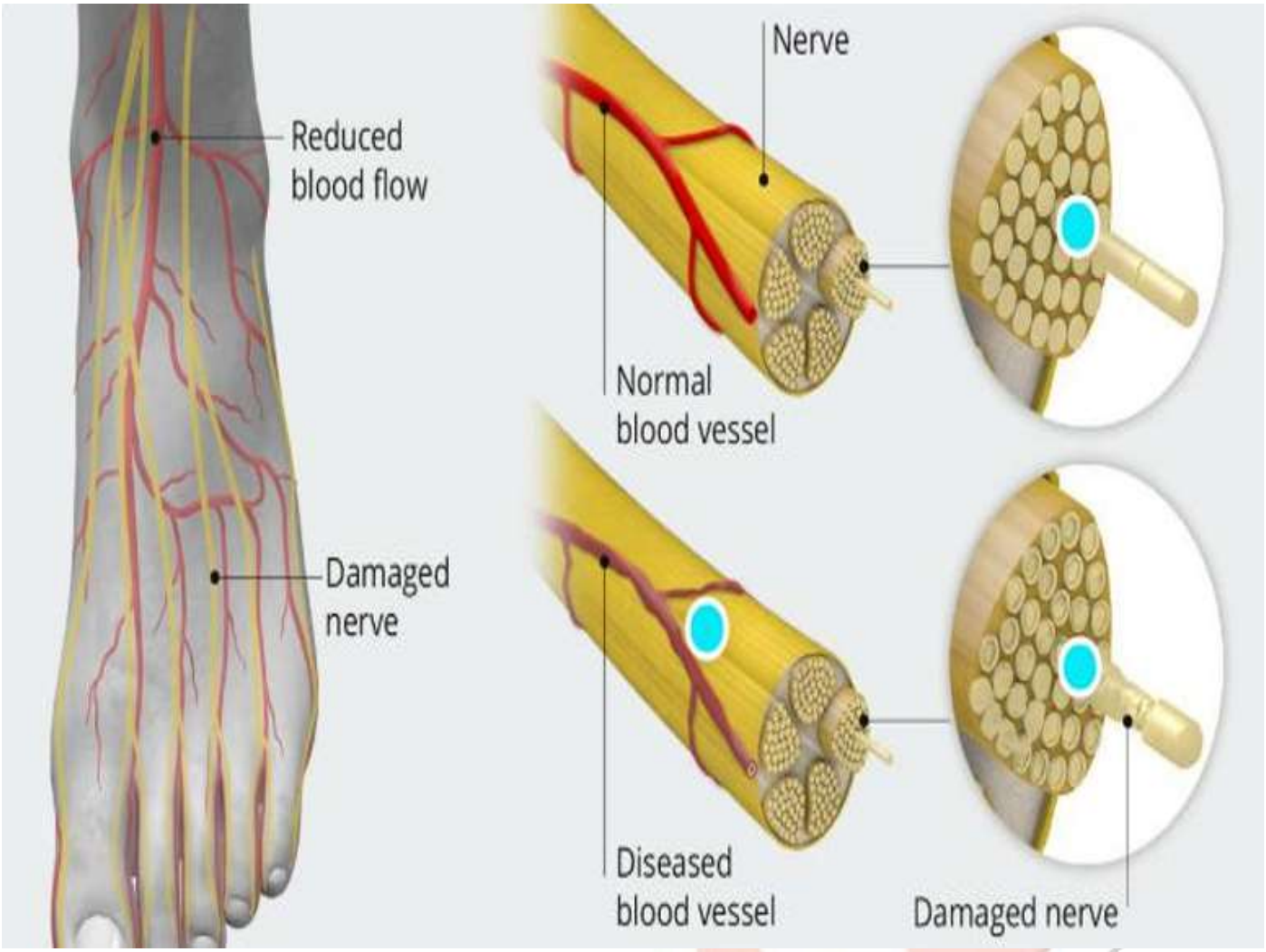
4.Complications of the Diabetes Mellitus

The long-term complications of diabetes mellitus mainly affect the blood vessels, nerves, eyes, kidneys, heart, and skin. These complications develop gradually due to prolonged high blood sugar levels and can be serious if not managed properly.

NEUROPATHIC COMPLICATIONS :

The most common form of neuropathy associated with diabetes mellitus is distal symmetric sensorimotor polyneuropathy, often accompanied by autonomic neuropathy. This disorder is characterized by striking atrophy and loss of myelinated and unmyelinated fibers accompanied by Wallerian degeneration, segmental, and paranodal demyelination and blunted nerve fiber regeneration. In both humans and laboratory animals, this progressive nerve fiber damage and loss parallels the degree and/or duration of hyperglycemia. Several metabolic mechanisms have been proposed to explain the relationship between the extent and severity of hyperglycemia and the development of diabetic neuropathy. One mechanism, activation of the polyol pathway by glucose via AR, is a prominent metabolic feature of diabetic rat peripheral nerve, where it promotes sorbitol and fructose accumulation, myo-inositol depletion, and slowing of nerve.

conduction by alteration of neural Na+-K+-ATPase activity or perturbation of normal physiological osmoregulatory mechanisms. ARIs, which normalize nerve myo-inositol and nerve conduction slowing, are currently the focus of clinical trials. Other specific metabolic abnormalities that may play a role in the pathogenesis of diabetic neuropathy include abnormal lipid or amino acid metabolism, superoxide radical formation, protein glycation, or potential blunting of normal neurotrophic responses. Metabolic dysfunction in diabetic nerve is accompanied by vascular insufficiency and nerve hypoxia that may contribute to nerve fiber loss and damage. Although major questions about the pathogenesis of diabetic neuropathy remain unanswered and require further intense investigation, significant recent progress is pushing us into the future and likely constitutes only the first of many therapies directed against one or more elements of the complex pathogenetic process responsible for diabetic neuropathy.



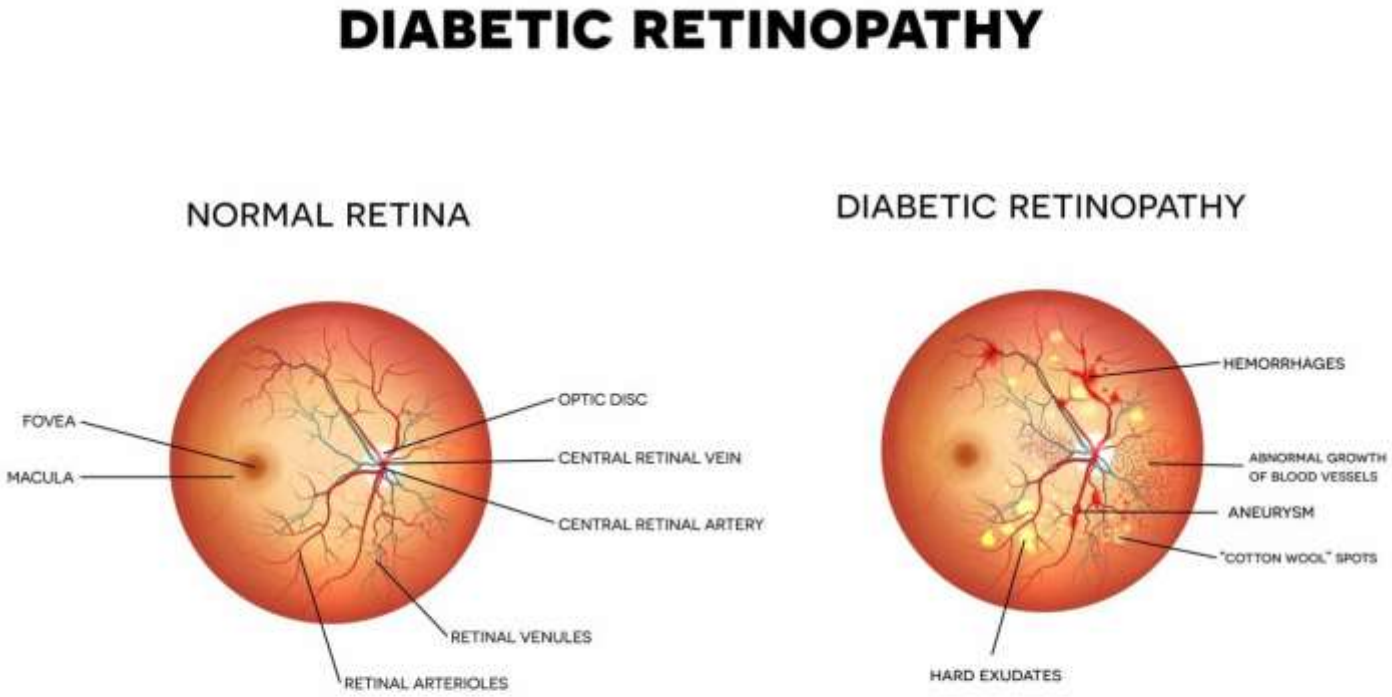
RETINOPATHIC COMPLICATIONS :

In industrialized nations diabetic retinopathy is the most frequent microvascular complication of diabetes mellitus and the most common cause of blindness in the working-age population. In the next 15 years, the number of patients suffering from diabetes mellitus is expected to increase significantly. By the year 2030, about 440 million people in the age-group 20-79 years are estimated to be suffering from diabetes mellitus worldwide (prevalence 7.7%), while in 2010 there were 285 million people with diabetes mellitus (prevalence 6.4%). Main reasons for loss of vision in patients with diabetes mellitus are diabetic macular edema and proliferative diabetic retinopathy.

Incidence or progression of these potentially blinding complications can be greatly reduced by adequate control of blood glucose and blood pressure levels. Diabetic retinopathy is a potentially blinding complication of diabetes mellitus. In patients with diabetes, regular retinal exams are essential. While laser photocoagulation is effective, if performed in time, advanced stages of diabetic retinopathy need to be treated by vitreo-retinal surgery and have limited visual prognosis. Even though new therapeutic options such as intravitreal medical therapy and sutureless pars-plana vitrectomy have improved ophthalmic care of patients with diabetes, interdisciplinary care of these patients is essential. Good metabolic and blood pressure control is indispensable for reducing the risk of ophthalmic complications. Micro-angiopathy due to hyperglycemia in patients with diabetes mellitus results in vascular leakage, which causes diabetic macular edema on one hand, and capillary occlusion on the other hand. Capillary occlusion then again causes retinal ischemia and increased levels of vascular endothelial growth factor (VEGF) which are responsible for the development of neovascularization and the proliferative stage of diabetic retinopathy.

More recently new pathways which may be involved in the pathogenesis of diabetic retinopathy have been identified, such as inflammation, nerve growth factor autophagy and epigenetics. A detailed discussion of all these pathways would go beyond the scope of this mini-review about clinical aspects of diabetic retinopathy, however some aspects should be addressed. Biochemical alterations such as oxidative stress, activation of protein kinase C and formation of advanced glycation end products have been detected as a response of the retina to hyperglycemial. Also kinin B1 and B2 are thought to increase vascular permeability, infiltration of

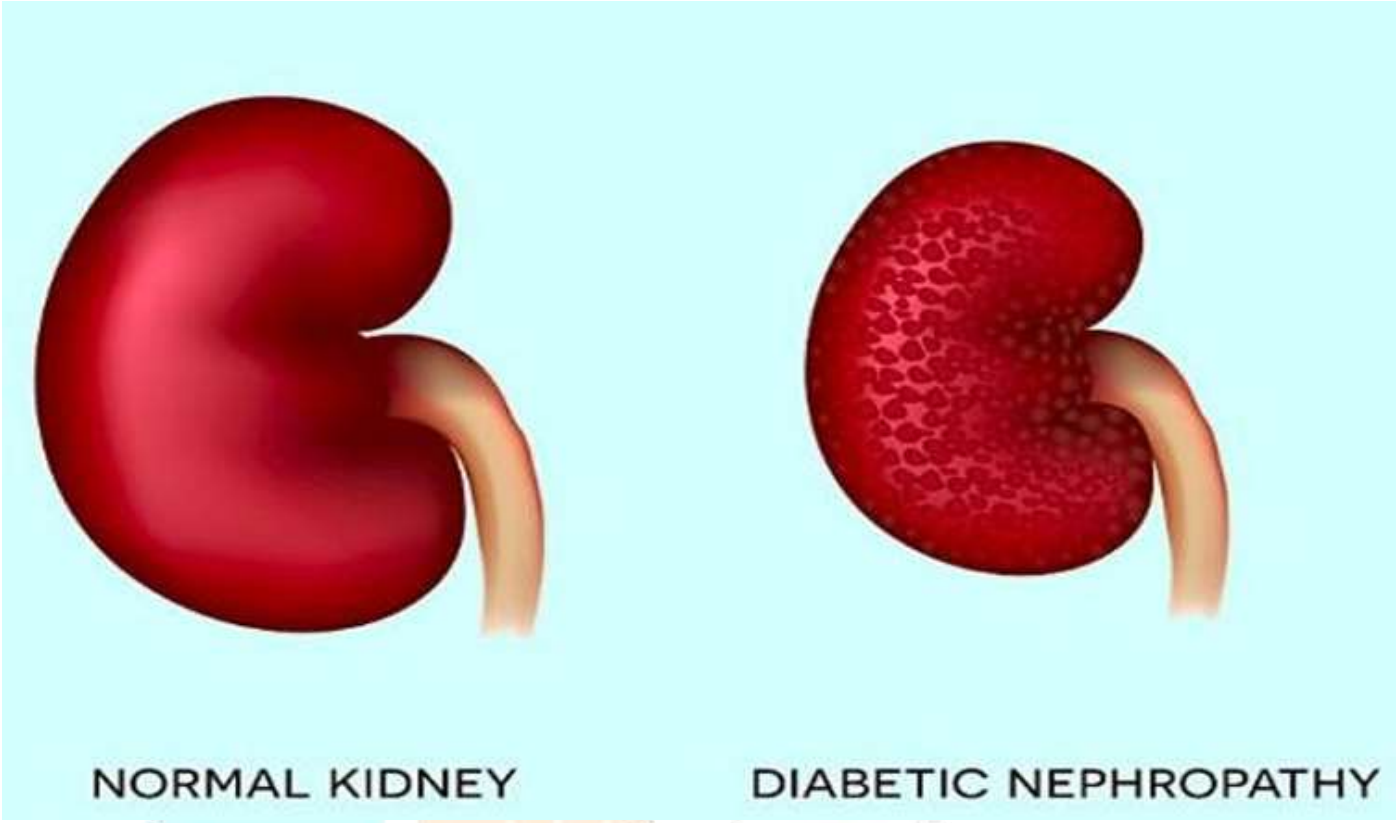
leukocytes and inflammation. Especially kinin B1, which is almost non-existent in normal tissue, is upregulated in the retina of diabetic patients.



NEPHROPATHIC COMPLICATIONS :

Diabetic nephropathy (DN) is the most prevalent diabetes associated in the complication of cardiovascular disorders. It is a major cause of cardiovascular mortality. It will impair the renal function of diabetes mellitus patients. The number of patients with chronic kidney disease (CKD) developing to end-stage renal disease (ESRD) and required renal replacement therapy, is increasing all over the world. Chronic Kidney disease affects over 20 million adults in the USA and over 13 million adults in Japan. Glomerular damage has to progress to clinical albuminuria with GFR 40–59 ml per minute. Due to AGEP, basement membrane will be thicken. Urine will be dipstick positive and containing more than 300 mg of albumin in a period of 24 h. Diabetic nephropathy has been determined into stages: microalbuminuria and macroalbuminuria.

The cut-off values of micro- and macroalbuminuria are arbitrary and their values have been questioned. Subjects in the upper-normal range of albuminuria seem to be at high risk of progression to micro- or macroalbuminuria and they also had a higher blood pressure than normoalbuminuric subjects in the lower normoalbuminuria range. Diabetic nephropathy screening is made by measuring albumin in spot urine. If it is abnormal, then it should be confirmed in two out three samples collected in a three to six-months interval. Additionally, it is recommended that glomerular filtration rate is routinely estimated for appropriate finding of nephropathy, some patients present a decreased glomerular filtration rate when urine albumin values are in the normal range. Glomerular damage continues with increase in amount of protein albumin in the urine.kidneys filtering ability is to be decrease steadily. Blood urea nitrogen BUN and creatinine Cr increase steadily. Hypertension (high blood pressure) increase in 3rd stage.



5. MANGIFERA INDICA :

Mangifera indica, commonly used herb in ayurvedic medicine. Although review articles on this plant are already published, but this review article is presented to compile all the updated information on its phytochemical and pharmacological activities, which were performed widely by different methods. Studies indicate mango possesses antidiabetic, anti-oxidant, anti-viral, cardiotonic, hypotensive, anti-inflammatory properties. Various effects like antibacterial, anti fungal, anthelmintic, anti parasitic, anti tumor, anti HIV, antibone resorption, antispasmodic, antipyretic, antidiarrhoeal, antiallergic, immunomodulation, hypolipidemic, anti microbial, hepatoprotective, gastroprotective have also been studied. These studies are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using mango for a variety of conditions should also be conducted. Mangifera indica (MI), also known as mango, aam, it has been an important herb in the Ayurvedic and indigenous medical systems for over 4000 years. Mangoes belong to genus Mangifera which consists of about 30 species of tropical fruiting trees in the flowering plant family Anacardiaceae. According to ayurveda, varied medicinal properties are attributed to different parts of mango tree. Mango is one of the most popular of all tropical fruits. Mangiferin, being a polyphenolic antioxidant and a glucosyl xanthone, it has strong antioxidant, anti lipid peroxidation, immunomodulation, cardiotonic, hypotensive, wound healing, antidegenerative and antidiabetic activities. Various parts of plant are used as a dentrifrice, antiseptic, astringent, diaphoretic, stomachic, vermifuge, tonic, laxative and diuretic and to treat diarrhea, dysentery, anaemiaasthma,bronchitis, cough, hypertension, insomnia, rheumatism, toothache, leucorrhoea, haemorrhage and piles.

6.TAXONOMICAL CLASSIFICATION :

Kingdom : Plantea
Class : Mangoliopsida
Phylum : Mangoliophyta
Order : Sapindales
Family : Anacardiaceae
Genus : Mangifera
Species : Indica

7.BOTINICAL DISCRIPTION :

Tree: MI is a big evergreen tree from the Anacardiaceae family. It grows very tall, about 10 to 45 meters, with a dome-shaped top and many strong branches coming from a thick trunk.

Leaves: The leaves grow in a spiral pattern on the branches. They are long, narrow, and pointed at both ends. Most are about 25 cm long and 8 cm wide, but some can be bigger. When young, they are reddish, soft, and give off a nice smell when crushed.

Flowers: The tree produces flowers in large clusters called panicles, with around 3000 tiny flowers. These flowers are whitish-red or yellowish-green.

Fruit: The fruit is large and fleshy (like a mango). It comes in many shapes and sizes, has thick yellow pulp, a single seed, and yellowish-red skin when ripe.

Seed: Inside the fruit is one seed, oval or oblong in shape, protected by a hard, fibrous shell.

8.HABITAT :

It is native tropical Asia and has been cultivated in the Indian subcontinent for over 4000 years and is now found naturalized in most tropical countries. Parts used: Roots, bark, leaves, fruits, seeds, flowers and kernels are used. Synonyms

Sanskrit: Ambrah; Madhuulii; Madhuula; Madhuulaka; English: Mango; Hindi: Aam; French: mangot; mangue; manguier; Portuguese: manga; mangueira; Dutch: manja; Tamil: Ambiram; Mambazham; Mambalam; Mangai; Punjabi: Amb; Wawashi; Gujarati: Ambo, Keri; Marvo (unripe); Kashmiri: Amb; Malayalam: Amram; Choothaphalam; Manga; Manpalam; Mavu; Marathi: Amchur; Amba.

8.PHYTOCHEMISTRY :

Chemical constituents of MI are always of an interest. The different chemical constituents of the plant, especially the polyphenolics, flavonoids, triterpenoids. Mangiferin a xanthone glycoside major bio-active constituent, isomangiferin, tannins & gallic acid derivatives. The bark is reported to contain protocatechic acid, catechin, mangiferin , alanine, glycine, γ aminobutyric acid, kinic acid, shikimic acid and the tetracyclic triterpenoids cycloart-24-en 3β,26diol, 3-ketodammar-24 (E)en-20S,26-diol, C-24 epimers of cycloart-25 en 3β,24,27-triol and cycloartan-3β,24,27-triol. Indicoside A and B, manghopanal, mangoleanone, friedelin, cycloartan-3β30-diol and derivatives, mangsterol, manglupenone, mangocoumarin, ntetacosane, n-heneicosane, n-triacontane and mangiferolic acid methyl ester and others isolated from stem bark of MI. Mangostin, 29-hydroxy mangiferonic acid and mangiferin have been isolated from the stem bark together with common flavonoids. The flower yielded alkyl gallates such as gallic acid, ethyl gallate, methyl gallate, n-propyl gallate, n-pentyl gallate, noctyl gallate, 4-phenyl gallate, 6-phenyl-n-hexyl gallate and dihydrogallic acid.

Root of mango contains the chromones, 3-hydroxy-2-(4'methylbenzoyl)-chromone and 3 methoxy-2-(4'-methyl benzoyl)-chromone. The leaf and flower yield an essential oil containing humulene, elemene, ocimene, linalool, nerol and many others. The fruit pulp contains vitamins A and C, β-carotene and xanthophylls. An unusual fatty acid, cis-9, cis-15-octadecadienoic acid was isolated from the pulp lipids of mango. Phenolic Antioxidants, Free Sugars and Polyols isolated and analyzed from Mango (MI) Stem Bark. All structures were elucidated by ES-MS and NMR spectroscopic methods. Quantitative analysis of the compounds has been performed by HPLC, and mangiferin was found to be the predominant component. Polyphenols have been characterized in mango puree concentrate by HPLC with diode array and mass spectrometric detection. A rapid method was developed for quantitative determination of beta-carotene, including cisisomers, in dried mango. HPLC method was developed to determine carotenoids in Taiwanese mango. 5-Alkyl- and 5-alkenylresorcinols, as well as their hydroxylated derivatives, extracted from mango (MI) peels, purified on polyamide and characterized by high-performance liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (HPLC/APcI-MS) for the first time.

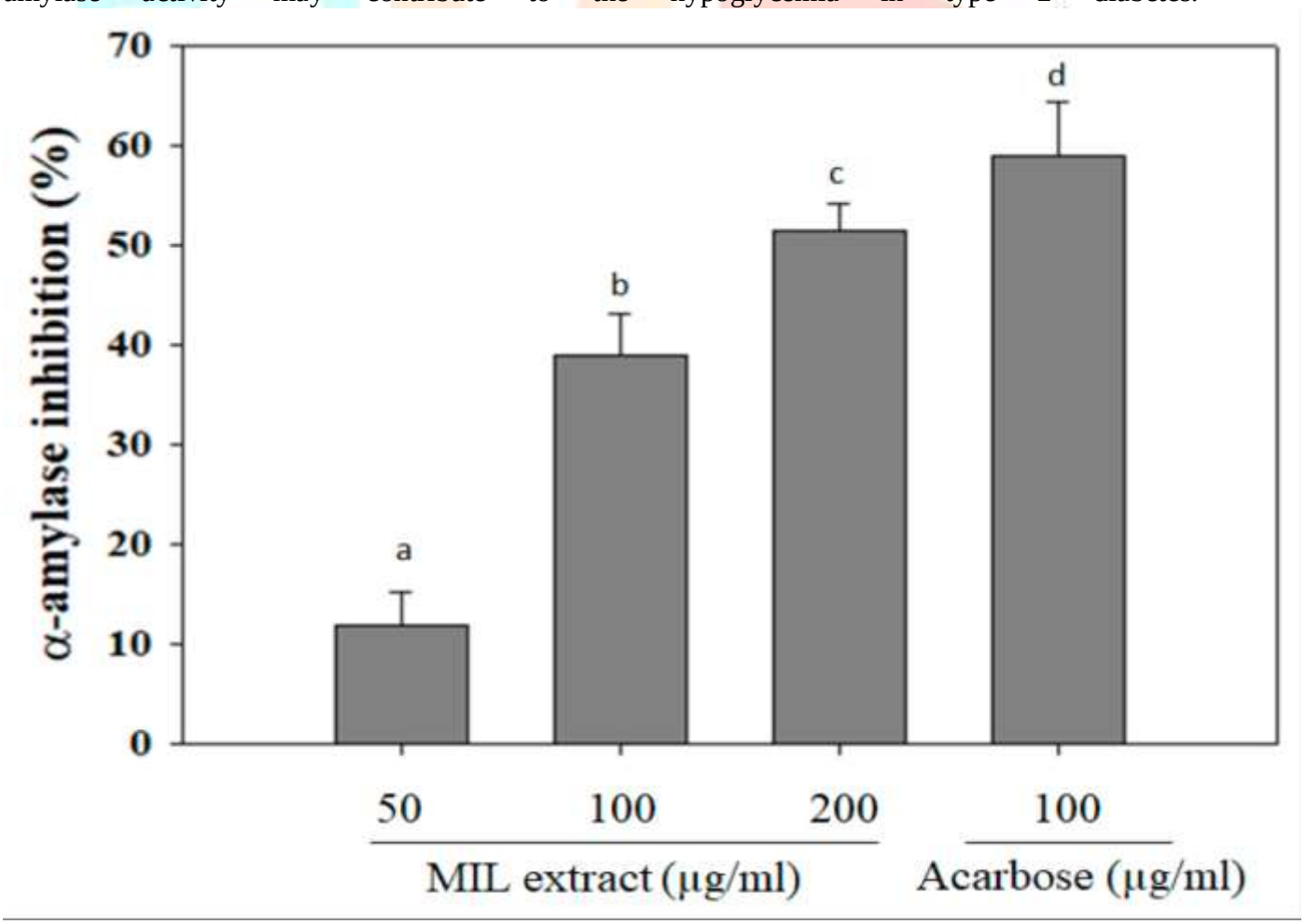
9.DISCUSSION:

Mechanism of Action of Mangifera indica Leaves for Anti-Diabetic Activity:

Alph a-Amylase Inhibitory Activity : Alpha-amylase is the most important digestive enzyme that catalyzes the hydrolysis of alpha-1,4 glycosidic linkages of carbohydrates. It cleaves the large starch molecules into smaller fragments of sugars to cross the gut epithelium. In a healthy person, excess levels of sugar will be converted to energy sources. However, in some cases, high levels of blood glucose due to excess activity of alpha-amylase results in hyperglycemia .

Thus, the inhibition of alpha-amylase activity can reduce postprandial hyperglycemia and prevent the risk of diabetes development .In this study, ethanol extract of M. indica leaves (MIL) was investigated for its capability against alpha-amylase activity. The results showed that MIL extract significantly inhibited alpha-amylase activity in a dose dependent manner. The inhibitory effect was observed up to (51.4 ± 2.7)% at a concentration of 200 µg/mL.

Meanwhile, acarbose exhibited an inhibitory effect of (59 ± 5.3)% at a concentration of 100 µg/mL. This result indicates that the inhibitory ability of MIL extract on alpha-amylase was stronger than that of Momordica charantia (IC50 was 0.267 ± 0.024 mg/mL) and was less effective than that of Physalis angulata fruit extract (97.2% inhibition at 100 µg/mL) .
Currently, acarbose, miglito, and voglibose are common anti-diabetic drugs that mainly act by inhibiting carbohydrate digestive enzymes, such as α-amylase, sucrose, maltase, and α Moreover, mice treated with acarbose slowed their breakdown of sucrose and starch . Hence, the inhibitory effect of MIL extract on alpha-amylase activity may contribute to the hypoglycemia in type 2 diabetes.



α-amylase inhibitory activity of Mangifera indica leaves (MIL) extract. The extract was pre-incubated with α-amylase for 30 min before adding starch solution. Reaction was stopped by DNS reagent and boiled for 5 min. Absorbance was measured at 540 nm. Acarbose was used as a positive control. Each determination

was made in three independent experiments, and the data are shown as means ± SD. Different letters a–d indicate significant difference among groups ($p < 0.05$) by Duncan's multiple-range test.

11.CONCLUSION :

Herbal plants are a huge source of potential bioactive components for therapy and management of diabetes. Here in, M. indica leaf extract has been evidenced as a promising anti-diabetic agent by inhibiting starch digestive enzyme, possessing glucose adsorption and glucose uptake capacity, suppressing NO production, and scavenging free radicals. Although the activities of commercial drugs were observed to be stronger than M. indica leaf extract, the potential hypoglycemic and antioxidant activities of M. indica leaves extract, evidenced in the present study, could be beneficial for type 2 diabetic patients. Hence, the present study provided useful evidence for the development of a functional hypoglycemic product from M. indica leaves. However, further studies related to the safety and efficacy need to be evaluated for long-term use of M. indica leaves.

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