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DIABETIC COMPLICATIONS: THE BAD AND GOOD SIDE OF DIABETES

SHABANA KHATOON [1*]

1*FACULTY OF PHARMACY, INTEGRAL UNIVERSITY, LUCKNOW.

1*CORRESPONDING AUTHOR: SHABANA KHATOON

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ABSTRACT

Human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to defect in insulin secretion, insulin action or both. Scientific reports revealed that diabetes cannot be cured completely. In addition to that rapid increase in diabetes mellitus is becoming a serious threat to mankind in all parts of the world. Medicinal plants play an important role in management of diabetes mellitus. Herbal medicines have shown good clinical practice in the therapy of diabetic mellitus. The present review gives detailed information about diabetes mellitus.

Diabetes mellitus has been a major health concern since several past decades. Cases of Type 1 as well as types 2 diabetes are increasing day by day. The major morbidity caused in the diabetic patients is due to dysfunction of several organ systems after a few years of having diabetes. Research has now clearly proved that these organ dysfunctions have their roots in diabetic pathophysiology. It has been shown that inflammation plays an important role in microvascular as well as macrovascular complications of diabetes. However, very less literature is available about methods used for evaluation of inflammation in diabetic complications. In this review we focus on role of inflammation in various diabetic complications.

Keywords: Diabetes mellitus, Diabetic complications, Herbal treatment

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to defect in insulin secretion, insulin action or both. Over the last century human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health. According to WHO statistics diabetes is the sixth leading cause of disease-related death in the world. On long standing it leads to many micro and macro vascular complications. it leads to many micro and macro vascular complications.

Diabetes mellitus, especially type-2 diabetes, is a public health problem which has reached epidemic proportions due to the rapidly increasing rates of this disease worldwide. Target organ complications, secondary to diabetes, are one of the most important medical concerns of the present time.[19].

The diabetes epidemic more pronounced in india as the World health organization (WHO) reports show that 32 million people had diabetes in the year 2000 (Wild S. et al.,2000). The International Diabetes Federation (IDF) estimates the total number of diabetic subject to be around 40.9 million in india and this is further set to rise to 69.9 million by the year 2025.[2,4].

The world prevalence of diabetes in 2010 among adults aged 20-79 years is estimated to 6.4%, affecting 285 million adults. Between 2010 and 2030, there is an expected 70% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. Each year more than 231,000 people in the United states and more than 3,96 million people worldwide die from diabetes and its complications. This number is expected to increase by more than 50 percent over next decade.[35].

Complications

Diabetes mellitus also causes "micro vascular" complications leading to the small blood vessels damage. Diabetic retinopathy, affects blood vessel formation in the retina of the eye, can lead to problems in vision like reduced vision, and potential blindness. Diabetic nephropathy, the complication of diabetes on the kidneys can lead to drastic changes in the kidney tissue, loss of progressively larger amounts of protein in the urine, and gradually leading to chronic kidney disease requiring dialysis. Diabetic neuropathy is the complication of diabetes effecting the nervous system, most commonly causing numbness, and pain in the feet and also increasing the risk of skin damage due to altered sensation. Diabetic neuropathy is a vascular disease effecting circulation of blood in the legs, contributing to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that are difficult to treat and occasionally require amputation[14].

Type 1 diabetes increases the risk for many serious health complications. However, during the past several decades, the rate of serious complications among people with diabetes has been decreasing, and more patients are living longer and healthier lives. There are two important approaches to preventing complications from type 1 diabetes.Good control of blood glucose and keeping glycosylated hemoglobin (A1C) levels below or around 7%. This approach can help prevent complications due to vascular (blood vessel) abnormalities and nerve damage (neuropathy) that can cause major damage to organs, including the eyes, kidneys, and heart.

Managing risk factors for heart disease. Blood glucose control helps the heart, but it is also very important that people with diabetes control blood pressure, cholesterol levels, and other factors associated with heart disease. [15].

These are 2 types (1) Micro vascular (2) Macro vascular

Micro vascular

Kidney Damage (Nephropathy) Kidney disease (nephropathy) is a very serious complication of diabetes. With this condition, the tiny filters in the kidney (called glomerul) become damaged and leak protein into the urine. Over time this can lead to kidney failure. Urine tests showing microalbuminuria (small amounts of protein in the urine) are important markers for kidney damage. [12,17].Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD). Patients with ESRD have 13 times the risk of death compared to other patients with type 1 diabetes. [22,24]. If the kidneys fail, dialysis or transplantation is required. Symptoms of kidney failure may include swelling in the feet and ankles, itching, fatigue, and pale skin color. The outlook of end-stage renal disease has greatly improved during the last four decades for patients with type 1 diabetes, and fewer people with type 1 diabetes are developing ESRD. [23,25].

Neuropathy

Diabetes reduces or distorts nerve function, causing a condition called neuropathy. Neuropathy refers to a group of disorders that affect nerves. The two main types of neuropathy are:

Peripheral (affects nerves in the toes, feet, legs, hand, and arms)

Autonomic affects nerves that help regulate digestive, bowel, bladder, heart, and sexual function Peripheral neuropathy particularly affects sensation. It is a common complication for nearly half of people who have lived with type 1 or type 2 diabetes for more than 25 years. The most serious consequences of neuropathy occur in the legs and feet and pose a risk for ulcers and, in unusually severe cases, amputation. Peripheral neuropathy usually starts in the fingers and toes and moves up to the arms and legs (called a stocking-glove distribution). Symptoms include:

Tingling, weakness, Burning sensations ,Loss of the sense of warm or cold, numbness (if the nerves are severely damaged, the patient may be unaware that a blister or minor wound has become infected),deep pain. Autonomic neuropathy can cause: Digestive problems (such as constipation, diarrhea, nausea, and vomiting), Bladder infections and incontinence, Erectile dysfunction. Heart problems. Neuropathy may mask angina, the warning chest pain for heart disease and heart attack. Patients with diabetes should be aware of other warning signs of a heart attack, including sudden fatigue, sweating, shortness of breath, nausea, and vomiting.[14,28].

Rapid heart rates, Lightheadedness when standing up (orthostatic hypotension)

Diabetic gastro paresis is a type of neuropathy that affects the digestive track. It is triggered by high blood sugar, which over time can damage the vagus nerve. The result of this damage is that the digestive system takes too long at time to move and empty food. Undigested food and the delay in stomach emptying can cause blood glucose levels to rise, and make diabetes more difficult to control. Symptoms of gastro paresis include heartburn, nausea, abdominal bloating, feeling full after eating only a small amount of food, and vomiting of undigested food several hours after a meal. Blood sugar control is an essential component in the treatment for neuropathy. Studies show that tight control of blood glucose levels delays the onset and slows progression of neuropathy. Heart disease risk factors may increase the likelihood of developing neuropathy. Lowering triglycerides, losing weight, reducing blood pressure, and quitting smoking may help prevent the onset of neuropathy.[29,32].

Foot Ulcers and Amputations

About 15% of patients with diabetes have serious foot problems. They are the leading cause of hospitalizations for these patients. The consequences of both poor circulation and peripheral neuropathy make this a common

and serious problem for all patients with diabetes. Diabetes is responsible for more than half of all lower limb amputations performed in the U.S. Most amputations start with foot ulcers.People with diabetes who are overweight, smokers, and have a long history of diabetes tend to be at most risk. People who have the disease for more than 20 years and are insulin-dependent are at the highest risk. Related conditions that put people at risk include peripheral neuropathy, peripheral artery disease, foot deformities, and a history of ulcers.Foot ulcers usually develop from infections, such as those resulting from blood vessel injury. Numbness from nerve damage, which is common in diabetes, compounds the danger since the patient may not be aware of injuries. About one-third of foot ulcers occur on the big toe. [11].

Charcot Foot Charcot foot or Charcot joint (medically referred to as neuropathic arthropathy) is a degenerative condition that affects the bones and joints in the feet. It is associated with the nerve damage that occurs with neuropathy. Early changes appear similar to an infection, with the foot becoming swollen, red, and warm. Gradually, the affected foot can become deformed. The bones may crack, splinter, and erode, and the joints may shift, change shape, and become unstable. It typically develops in people who have neuropathy to the extent that they cannot feel sensation in the foot and are not aware of an existing injury. Instead of resting an injured foot or seeking medical help, the patient often continues normal activity, causing further damage.

Retinopathy and Eye Complications

Diabetes accounts for thousands of new cases of blindness annually and is the leading cause of new cases of blindness in adults ages 20-74. The most common eye disorder in diabetes is retinopathy. People with diabetes are also at higher risk for developing cataracts and certain types of glaucoma.[26].Retinopathy is a condition in which the retina becomes damaged. It generally occurs in one or two phases: The early and more common type of this disorder is called *non* proliferative or background retinopathy. The blood vessels in the retina are abnormally weakened. They rupture and leak, and waxy areas may form. If these processes affect the central portion of the retina, swelling may occur, causing reduced or blurred vision.[10,16]. If the capillaries become blocked and blood flow is cut off, soft, "woolly" areas may develop in the retina's nerve layer. These woolly areas may signal the development of proliferative retinopathy. In this more severe condition, new abnormal blood vessels form and grow on the surface of the retina. They may spread into the cavity of the eye or bleed

into the back of the eye. Major hemorrhage or retinal detachment can result, causing severe visual loss or blindness. The sensation of seeing flashing lights may indicate retinal detachment.[21].

Diabetes mellitus comes from the Greek word "diabainein" meaning "to pass through," and the Latin word "mellitus" meaning "sweetened with honey." Put the two words together and you have "to pass through sweetened with honey."[17, 22].

Macro vascular

Heart Disease and Stroke

Patients with type 1 diabetes are 10 times more at risk for heart disease than healthy patients. Heart attacks account for 60% of deaths in patients with diabetes, while strokes account for 25% of such deaths. Diabetes affects the heart in many ways:

Both type 1 and 2 diabetes accelerate the progression of atherosclerosis (hardening of the arteries). Diabetes is often associated with low HDL ("good" cholesterol) and high triglycerides. This can lead to coronary artery disease, heart attack, or stroke. In type 1 diabetes, high blood pressure (hypertension) usually develops if the kidneys become damaged. High blood pressure is another major cause of heart attack, stroke, and heart failure. Children with diabetes are also at risk for hypertension. Impaired nerve function (neuropathy) associated with diabetes also causes heart abnormalities. Atherosclerosis is a disease of the arteries in which fatty material is deposited in the vessel wall, resulting in narrowing and eventual impairment of blood flow. Severely restricted blood flow in the arteries to the heart muscle leads to symptoms such as chest pain. Atherosclerosis shows no symptoms until a complication occurs.[29].

Hyperglycemia hyperosmolar state

Hyperosmolar nonketotic state (HNS) is an acute complication sharing many symptoms with DKA, but an entirely different origin and different treatment. A person with very high (usually considered to be above 300 mg/dl (16 mmol/L)) blood glucose levels, water is osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine. This results in loss of water and an increase in blood osmolarity. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels, combined with the loss of water, will eventually lead to dehydration. The body's cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and are always

dangerous. As with DKA, urgent medical treatment is necessary, commonly beginning with fluid volume replacement. Lethargy may ultimately progress to a coma, though this is more common. in type 2 diabetes than type 1.

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute and dangerous complication that is always a medical emergency and requires prompt medical attention. Low insulin levels cause the liver to turn fatty acid to ketone for fuel (i.e., ketosis); ketone bodies are intermediate substrates in that metabolic sequence. This is normal when periodic, but can become a serious problem if sustained. Elevated levels of ketone bodies in the blood decrease the blood's pH, leading to DKA. On presentation at hospital, the patient in DKA is typically dehydrated, and breathing rapidly and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy may progress to coma. Ketoacidosis can easily become severe enough to cause hypotension, shock, and death. Urine analysis will reveal significant levels of ketone bodies (which have exceeded their renal threshold blood levels to appear in the urine, often before other overt symptoms). Prompt, proper treatment usually results in full recovery, though death can result from inadequate or delayed treatment, or from complications (e.g., brain edema). Ketoacidosis is much more common in type 1 diabetes than type 2.[29].

Hypoglycemia

Hypoglycemia, or abnormally low blood glucose, is an acute complication of several diabetes treatments. It is rare otherwise, either in diabetic or non-diabetic patients. The patient may become agitated, sweaty, weak, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilized panic. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death. In patients with diabetes, this may be caused by several factors, such as too much or incorrectly timed insulin, too much or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (specifically glucose containing carbohydrates). The variety of interactions makes cause identification difficult in many instances.[30].

It is more accurate to note that iatrogenic hypoglycemia is typically the result of the interplay of absolute (or relative) insulin excess and compromised glucose counter regulation in type 1 and advanced type 2 diabetes. Decrements in insulin, increments in glucagon, and, absent the latter, increments in epinephrine are the primary glucose counter regulatory factors that normally prevent or (more or less rapidly) correct hypoglycemia. In insulin-deficient diabetes (exogenous) insulin levels do not decrease as glucose levels fall, and the combination of deficient glucagon and epinephrine responses causes defective glucose counter regulation.

Furthermore, reduced sympatho adrenal responses can cause hypoglycemia unawareness. The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent incidents of hypoglycemia cause both defective glucose counter regulation and hypoglycemia unawareness. By shifting glycemic thresholds for the sympatho adrenal (including epinephrine) and the resulting neurogenic responses to lower plasma glucose concentrations, antecedent hypoglycemia leads to a vicious cycle of recurrent hypoglycemia and further impairment of glucose counter regulation. In many cases (but not all), short-term avoidance of hypoglycemia reverses hypoglycemia unawareness in affected patients, although this is easier in theory than in clinical experience. In most cases, hypoglycemia is treated with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with effects largely opposite to those of insulin) or an intravenous infusion of dextrose is used for treatment, but usually only if the person is unconscious. In any given incident, glucagon will only work once as it uses stored liver glycogen as a glucose source; in the absence of such stores, glucagon is largely ineffective. In hospitals, intravenous dextrose is often used.[33].

Respiratory infections

The immune response is impaired in individuals with diabetes mellitus. Cellular studies have shown that hyperglycemia both reduces the function of immune cells and increases inflammation. The vascular effects of diabetes also tend to alter lung function, all of which leads to an increase in susceptibility to respiratory infections such as pneumonia and influenza among individuals with diabetes. Several studies also show diabetes associated with a worse disease course and slower recovery from respiratory infections.[1].

Diagnostic Methods of Diabetes

Diabetes mellitus is diagnosed by demonstrating any one of the following methods:

Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL)

Plasma glucose ≥ 11.1 mmol/L (200 mg/dL)

Glycated hemoglobin (Hb A1C) ≥ 6.5%

Oral glucose tolerance test (OGTT)

People with fasting glucose levels from 100 to 125 mg/dL are considered to have impaired fasting glucose also called as pre-diabetes. Fasting plasma glucose is mostly preferred because of its low cost and is very easy to operate.The 2-hour oral glucose tolerance test (OGTT) is a standard test for diagnosing type 2 diabetes but it is expensive the methods require patients to be tested in the fasted state. Glycated haemoglobin (HbA1c).Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause. [36,37].The most commonly used criteria to diagnose obesity are National Cholesterol Education Program (NCEP), ATP III criteria.The American Diabetes Association suggests that sudomotor function assessing small fiber status should be included in the diagnostic tests for the detection of neuropathies in diabetes [38].

Treatment

The treatment for diabetes mainly involves the regulation of blood sugar levels and to prevent diabetic complications. Medicines, diet, and exercise are included in treatment. Lifestyle modifications and oral anti-diabetic medications are recommended for initial treatment of DM [39].Insulin therapy is required for T1D because cells cannot produce insulin. Although cells produce insulin harmone in type 2 diabetes but they donot respond normally to insulin. In such cases insulin therapy helps cells to overcome the resistance to insulin.Continuous subcutaneous insulin infusion (CSII) is useful therapy for brittle T1D worldwide. The frequency of hypoglycemia was decreased and improved glycemic variability was achieved with CSII therapy which is beneficial to pregnant women with diabetes [40,41].

Insulin Types

The most commonly-used human insulin preparations are Regular (rapid onset of action, short duration of action) and NPH (slower onset of action, longer duration of action. Lente insulin also is insulin with an intermediate duration of action.Insulin lispro was developed by modification at the B26-30 regions of insulin. It

was approved by the FDA in June, 1996. It was absorbed faster and had a shorter duration of action: action started within 15 mins of injection, peaked by an hour and disappeared within four hours. When lispro was modified to a protamine formulation of neutral protamine lispro, it gave similar overall glycemic control,with improved postprandial glucose. Insulin aspart was developed by substituting proline with aspartic acid. It has the advantage of reducing the self-association and enhancing the absorption rate [42,43].

Insulin glargine was developed by elongating the C terminal of insulin B chain by two arginine residues: A21 aspargine residue was substituted with glycine. Insulin glargine has a slower onset of action (70 minutes) and a longer duration of action (24 hours) than regular human insulin. Its activity does not peak. Recent rapid acting insulin analogues include Insulin glulisine which is by derived from human insulin by the replcement of AspB3 by Lys and LysB29 by Glu. Both glulisine and lispro are absorbed faster than regular insulin and both displayed non-inferiority of glycemic control in all types of diabetes [43]. Insulin analogues have so many advantages, but they are not used more extensively because they are more expensive than regular insulins [42,44].

Intensive glycaemic control in type 2 diabetes remarkably reduces the risk of development of microvascular complications proved by the United Kingdom Prospective Diabetes Study (UKPDS).Riddle et al. [45] have reported that improved glycemic control accompanied by weight loss was achieved when pramlintide, an amylin analogue, was used in combination with insulin glargine.

Allen Nichol et al. [46] reported that by judicious use of these three drugs insulin glargine, U-500 insulin and pramlinitide, total number of drugs patient needed to control diabetes has been reduced from 5 to 3.

Based on the insulin mechanism of action, various drugs have been developed, called insulin secretagogues, which stimulate beta cells of pancreas for a) secretion of additional insulin e.g. sulphonylureas and b) insulin sensitizers e.g. metformin. The sensitizers increases action of the existing insulin and facilitate greater uptake of glucose from plasma. Hence they are called insulin sensitizers. Insulin sensitization is commonly understood as glucose clearance from plasma without addition al inputs of insulin. In contrast, insulin resistance is thought to be poor glucose clearance despite presence of high amounts of insulin. For insulin sensitization, metformin is a commonly used drug for treating T2D [47].

Metformin was approved by FDA in December 1994 [48]. Fiber foods and gums such as fenugreek seeds are found to bring glycemic control in diabetic subjects. Fiber because of its viscosity reduces circulating insulin levels [47,49].

Postprandial glucose excursions may be better controlled by adjusting the timing of prandial (bolus) insulin dose administration. The optimal time to administer prandial insulin varies, based on the type of insulin used (regular, rapid-acting analog, inhaled, etc.), measured blood glucose level, timing of meals, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized.

Pramlintide Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is FDA-approved for use in adults with type 1 diabetes. It has been shown to induce weight loss and lower insulin doses. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia[50].

Surgical treatment for Type one Diabetes

Pancreas and Islet Transplantation

Pancreas and islet transplantation have been shown to normalize glucose levels but require life-long immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management[51].

Oral hypoglycemic agents

Most widely used oral hypoglycemic agents include Sulfonylureas. Thiazolidinediones are widely used oral hypoglycemic agents which decrease glucose levels in type-2 diabetic patients by increasing the insulin sensitivity of target tissues. Metformin lowers blood glucose both by increasing insulin sensitivity and by decreasing hepatic gluconeogenesis. Metformin causes weight loss and a modest reduction in serum LDL cholesterol and triglyceride levels. [52]. Methadone has been used to manage chronic pain and also as an analgesic in diabetic neuropathy [53,54].

American Diabetes Association and The European Association for the Study of Diabetes recommended metformin as the first-line treatment for T2D. However, an annual failure of metformin therapy has been reported. Newer classes of agents are being developed with novel mechanisms of action: SGLT-2 inhibitors, longer acting GLP-1 agonists, and PPAR α/γ dual and pan-agonists. Imeglimin belongs to a new class of drugs

"the glimins" developed for the treatment of T2D with an objective to provide a safe and well-tolerated drug with unique pharmacological properties. Imeglimin has a different mechanism of action compared to other oral anti-diabetic compounds. Imeglimin is an innovative compound able to regulate multiple targets, including insulin resistant organs as well as β-cell failure [55].

In patients with T2DM Thiazolidinedione (TZD) therapy improves glycemic control both by strengthening beta cell function and enhancing tissue sensitivity to insulin by acting as peroxisome proliferator-activated receptor (PPAR) gamma agonists in liver and muscle. Insulin resistance and glucose intolerance was reduced with in time delivery of bromocriptine to the central nervous system. Bromocriptine-QR recently was approved by the US Food and Drug Administration (FDA) and is indicated as a supplement to diet and exercise to improve glycemic control in adults with T2DM. Bromocriptine-QR acts as insulin sensitizer. Current guidelines for T2DM treatment suggested initial therapy with metformin and/or sulfonylurea.The efficacy of present antihyperglycaemic agents is limited and most patients do not achieve glycated haemoglobin targets [56,57].

Two glucagon-like peptide 1 (GLP-1) analogues are approved for use in Canada- liraglutide and exenatide. Similarly, two DPP-4 inhibitors are currently in use in Canada: saxagliptin and sitigliptin. Both GLP-1 analogues and DPP-4 inhibitors stimulate insulin secretion, inhibit glucagon secretion in a glucose-dependent manner and have a low risk of hypoglycaemia. Despite having much less tolerability than DPP-4 inhibitors, GLP-1 analogues are exceptional in achieving significant weight loss and lower A1C levels [58,59]. Recently, a series of phosphonic acid-containing 4-aminobenzimidazoles were reported as adenosine-5'- monophosphate (AMP) mimics, function as inhibitors of fructose1,6-bisphosphatase (FBPase), and demonstrated in vivo glucose-lowering activities in rodent models of T2DM [60,61,62].

Herbal treatment for diabetes

Herbal treatment for diabetes

Bitter Gourd (Momordica charantia), Bael (Aegle marmelos), Gurmar Leaves (Gymnema sylvestrae), Fenugreek (Trigonella foenum graecum), Turmeric (Curcuma longa), Onion (Allium cepa), Nayantatra (Vinca rosa), Neem (Azadirachtha indica), Garlic (Allium sativum), and sagar gota (Ceasalpinia crista) are the most useful herbs for diabetic treatment. EA is a polyphenol naturally occurring in berries and nuts has shown many properties such as antioxidant, antimicrobial and antimutagenic agent [63,64].

Leaf extract of **Terminalia arjuna** (Combretaceae), an ayurvedic plant has recently been shown to possess antihyperglycemic activity in streptozotocin-induced diabetic rats. Several plant derived compounds have been

shown to activate glucose transport through leaf extract leaf extract AMP Activated Protein Kinase (AMPK) activation Ex: Berberine. Curcumin, a principal curcuminoid of turmeric, salidroside, a bioactive component from Rhodiola rosea and cryptotanshinone, a quinoid diterpene were also reported to have AMPK mediated stimulatory effect on glucose uptake in adipocytes and muscles [65]. The nutraceuticals developed from the soluble and fiber fractions of rice bran control both T1DM and T2DM.

Allium c epa *L., Bulbus Allium cepa* L. is a perennial herb belonging to the Amaryllidaceae. The parts of the plant used are the fresh or dried bulbs, commonly known as onion, which are commercially cultivated worldwide [66]. The main chemical constituents are sulfur-containing compounds, such as L-cysteine sulfoxides, and flavonoids, such as quercetin and its glycosides [67]. *A. cepa* exerts its antidiabetic activity through multiple pharmacologic actions attributed to the presence of many active constituents: for example, quercetin is responsible for α-glucosidase inhibition [68] and, along with rutin, for the increase of GLUT-4 translocation, glucose uptake and insulin action [69]. In fact, they take part in the redox process of glutathione and cysteine, and can also increase the activity of superoxide dismutase and catalase, independently or through the stimulation of insulin secretion [70,71].

Azadirachta indica *A. Juss., Folium Azadirachta indica* A. Juss., also known as neem, is a deciduous tree belonging to the Meliaceae. The parts of the plant used are the dried leaves [72]. It contains characteristic compounds, such as oxidized tetranotriterpenes, known as azadirachtins [73]. The main mechanism of action of azadirachtins (e.g., azadirachtolide, azadiradione, gedunin and meliacinolin) is the inhibition of α-amylase and α-glucosidase [74,75].

Momordica charantia *L., Fructus Momordica charantia* L. is a monoecious annual climbing vine belonging to the Cucurbitaceae. The parts of the plant used are the fresh or dried fruits, known as bitter melons [76]. The main chemical constituents are sterols, triterpenes and bioactive proteins [77]. Cucurbitane triterpenoids from *M. charantia* displayed hypoglycemic effect, reducing blood glucose levels, [78].

Ocimum tenuiflorum *L., Folium Ocimum tenuiflorum* L., commonly referred to as tulsi, is a herb or shrub up to 1 meter high belonging to the botanical family Lamiaceae. The main chemical components are tannins and essential oil (mainly composed of eugenol, methyleugenol, and α- and β-caryophyllene) [79]. Lowering blood glucose levels in normal, glucose fed hyperglycemic.

Panax Ginseng *C.A. Meyer, Radix and Panax quinquefolius L., Radix* Ginseng has been used in traditional Chinese medicine significant effects on purine, tryptophan, fatty acids and energy metabolism more effective

reduction of hyperglycemia, increase in insulin/glucose ratio and improvement. ginseng in lowering blood glucose, total cholesterol and triglycerides in streptozocin-induced diabetic rats [80].

Rehmannia glutinosa *(Gaertn.) DC., Radix Rehmannia glutinosa* (Gaertn.) DC. is a perennial herb belonging to the family Plantaginaceae. The parts of the plant used are the dried roots and rhizomas [81]. The main constituents are iridoid glycosides and monoterpenes [82]. Increase β-endorphin secretion; up-regulation of GLUT-4 expression Improvement of redox homeostasis; reduction of hepatic glucose-6-phosphatase activity; increase of hepatics glycogen level; reduction of ROS production; inhibition of NF-κB translocation; down-regulation of TNF-α, COX-2, MCP-1 and inducible protein-10

Trigonella foenum-graecum *L., Semen sTrigonella foenum-graecum* L., fenugreek, is an annual aromatic herb belonging to the family Fabaceae. The parts of the plant used are the dried ripe seeds, which contains mucilage and a variety of other secondary metabolites such as trigonelline [81]. The bioactive compounds which has been more deeply studied for the hypoglycemic actions are trigonelline, diosgenin, 4-hydroxyisoleucine and the soluble dietary fiber fraction of fenugreek seeds [83].

Cinnamon Botanical preparation of cinnamon may results from the dried inner bark of the shoots grown on cut stock of *Cinnamomum verum* J. Presl. as well as from the trunk bark, freed or cork of *Cinnamomum cassia* (L.)J. Presl., both species belonging to the family Lauraceae [66]. The parts of the plant used are the dried bark, free from the outer cork, which contains mainly cinnamaldehyde, eugenol and coumarin in concentrations that can vary abundantly between the two species [84]. Indeed, *C. verum* essential oil contains about 50–63% cinnamaldehyde and only traces of coumarins; *C. cassia* essential oil, instead, contains up to 95% cinnamaldehyde and up to 1% coumarins, together with an higher content of benzaldehyde and methoxycinnamaldehyde, compared to *C. verum.* coumarins to 0.1 mg/kg bw [85]. Considering the potential toxicity of coumarins in *C. cassia*, it can be speculated that *C. verum* may be safer for clinical application in chronic diseases requiring prolonged treatments, such as type 2 diabetes

Conclusions safety and biological effects of herbal products and many of the medicinal plants currently used to treat hyperglycemia, indeed, derive from traditional use. Medicinal plants possessing anti-diabetes activities, World regions and is supported by clinical evidence, are considered by WHO and enlisted in WHO monographs on medicinal plants. Cinnamon anti-diabetic activity lacks of authoritative support, but many clinical trials have been conducted in the last five years, suggesting an increasing interest concerning its

application in the management of diabetes**,** the use of herbal products often relies on the synergistic and multitarget effects of the phytocomplex, which may lead to a clinical effectiveness together with a lower incidence of adverse events [86].

REFERENCES

1. Kumar PJ, Clark M, et al. Textbook of Clinical Medicine. Pub: Saunders. 2002; 1099-1121.

2.Amos A, McCarty D, Zimmet P, et al.The rising global burden of diabetes and its complications. estimates and projections to the year 2010; Diabetic Med 1997; 14: 1 -85.

3.Navale AM, Paranjape AN, et al. Role of inflammation in development of diabetic complications and commonly used inflammatory markers with respect to diabetic complications. International Journal of Pharmacy and Pharmaceutical Sciences.2013; 5:1-5.

4.Kamboj A, et al.Diabetes mellitus or impaired glucose tolerance. Diabetology.2008; 201-203.

5. Katzung B,Masters S, Trevor A, et al. Basic and clinical pharmacology.2009; 11:727-749.

6.Tripathi KD,Essential of medical pharmacology, jaypee brother's medical publishers (p) ltd sixth edition, .2013; 7: 258-281.

7. Goodman and Gilman's, Manual of pharmacology and therapeutics.2008; 11:1037-1058.

8. Moran A, Palmas W, Field L, et al. Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. Diabetes care. 2004; 27: 972-977.

9. Huang C, Kim Y, Caramori ML, et al. Cellular basis of diabetic nephropathy II. The transforming growth factor-beta system and diabetic nephropathy lesions in type 1 diabetes. Diabetes 2002; 51: 3577-3581.

10 .Shukla N, Angelini GD, Jeremy JY, et al. Homocysteine as a risk factor for nephropathy and retinopathy in type 2 diabetes. Diabetologia. 2003; 46: 766-772.

11 .Wallace C, Reiber GE, Master J, et al. Incidence of falls risk factors for falls and fall-related factures in individuals with diabetes and a prior foot ulcer. Diabetes Care.2002; 25: 1983-1986.

12 .Nakagawa T, et al. Endothelial dysfunction as a potential contributor in diabetic nephropathy Nat. Rev. Nephrol.2010;152.

13.Sharma K, Ziyadeh FN, et al. Hyperglycemia and diabetic kidney disease. The case for transforming growth factor-beta as a key mediator. Diabetes.1995; 44: 1139-46.

14 .The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabete Control and Complications Trial Research Group". Annals of Internal Medicine.1995; 122 (8): 561–8.

15. Ramachandran A, Sneha latha C, Viswanathan V, et al. Burden of type 2 diabetes and its complications .The Indian scenario. Current Science. 2002; 83: 1471–1476.

16. Hove MN, Kristensen JK, Lauritzen T, Bek T, et al. The prevalence of retinopathy in an unselected population of type 2 diabetes patients from Arhus County, Denmark. Acta Ophthalmology Scand . 2004; 82: 443-448.

17. Shukla N, Angelini GD, Jeremy JY, et al. Homocysteine as a risk factor for nephropathy and retinopathy in type 2 diabetes. Diabetologia. 2003; 46: 766-772.

18. American Diabetes Association. Standards of medical care in diabetes. 2012. Diabetes Care. 2012 ; (35) 1:11-63.

19. Alemzadeh R, Wyatt DK, et al. Diabetes mellitus. In Kliegman RM, ed. Nelson Textbook of Pediatrics. 18th edition. Saunders. 2007: 590.

20. Clark A, Nilsson M.R, et al. Islet amyloid a complication of islet dysfunction or an aetiological factor in Type 2 diabetes. Diabetologia. 2004; 47:157–169.

21. Verma A, Shan ZY, Lei B,Yuan LH, Liu X, et al. ACE2 and Ang-(1–7) Confer Protection Against Development of Diabetic Retinopathy. Molecular Therapy.2012; 20: 28–36.

22. Liu C, Hu Q, Wang Y, Zhang W, Ma ZY, et al. Angiotensin-converting enzyme (ACE) 2 over expression ameliorates glomerular injury in a rat model of diabetic nephropathy a comparison with ACE inhibition.2011;17: 59–69.

23. Nadarajah R, Milagres R, Dilauro M, Gutsol A, Xiao F, et al. Podocyte-specific over expression of human angiotensin-converting enzyme 2 attenuates diabetic nephropathy in mice. Kidney Int. 2012; 82: 292–303.

24. Wang G, Lai FM, Lai KB, Chow KM, Kwan CH, Urinary mRNA expression of ACE and ACE2 in human type 2 diabetic nephropathy. Diabetologia.2008; 51: 1062–1067.

25. Mizuiri S, Aoki T, Hemmi H, Arita M, Sakai K, et al. Urinary angiotensin-converting enzyme 2 in patients with CKD. Nephrology.2011; 16: 567–572.

26. Fong DS, Aiello LP, Ferris FL, et al. Diabetic retinopathy. Diabetes Care.2004; 27:2540–2553.

27. Gabbay KH, et al. Hyperglycemia polyol metabolism and complications of diabetes mellitus. Annu Rev Med. 1975; *26:521*–536.

28. Gabbay KH, et al. Aldose reductase inhibition in the treatment of diabetic neuropathy where are we in *Curr Diab Rep.2004;* 4:405–408.

29. Kunisaki M, Bursell SE, Clermont AC, Ballas LM, Jirousek MR, Umeda F., Nawata H.,King GL, et al.Vitamin E prevents diabetes-induced abnormal retinal blood flow via the diacylglycerol proteinkinase C pathway. Am J Physiol.*1995;* 269:239–246.

30 .U.K.Prospective Diabetes Study Group Tight blood pressure control and risk of macrovascular and microvascular complications in type 2diabetes. *BMJ*. 1998; 317:703–713.

31. American Diabetes Association Standards of medical care in diabetes. Diabetes Care.*2007;* 30: 4–41.

32. Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D, et al. Diabetic neuropathies a statement by the American Diabetes Association. Diabetes Care.*2005;* 28:956–962.

33. Boyle PJ, et al. Diabetes mellitus and macrovascular disease mechanisms and mediators. Am J Med *2007;* 120:12–17.

34. Beckman JA, Creager MA, Libby P, et al. Diabetes and atherosclerosis epidemiology pathophysiology and management. JAMA.*2002;* 287:2570–2581.

35. Arunachalam K, et al. Evaluated the effect of methanolic extract of the bark of Ficus amplissim on streptozotocin-induced diabetic rats. Journal of Ethanopharmacology. 2013;147: 302-310.

36.Reddigan JI, Ardern CI, Riddell MC, Kuk JL (2010) Differences in the Association between Clinically Relevant Classifi cations of Glycemia Measures and All-Cause and Cardiovascular Disease Mortality Risk. J Diabetes Metab 1:106.

37.Goldstein DE, Little RR, Lorenz RA (2004) Tests of glycemia in diabetes. Diabetes Care 27: 1761-1773.

38.Ramachandran A, Moses A, Snehalatha C, Shetty AS, Seeli AC, et al.(2011) Assessment of Sudomotor Function to Predict Future Abnormalities of Glucose Tolerance in at Risk Population. J Diabetes Metab 2:125.

39.Esteghamati A, Nakhjavani M, Aminorroaya A, Aboutorabi R, M Niafar, et al. (2011) Biphasic Insulin Aspart 30 (BIAsp 30) is Safe and Improves Glycaemic Control in Insulin Naïve Patients with Type 2 Diabetes. J Diabetes Metab 2:123.

40.Higuchi C, Tone A, Iseda I, Tsukamoto K, Katayama A, et al. (2010) A Pregnant Patient with Brittle Type 1 DiabetesSuccessfully Managed by CSII Therapy with Insulin Aspart. J Diabetes Metab 1:104.

41.Lenhard MJ, Reeves GD (2001) Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. Arch Intern Med 22: 2293-2300.

42. Sridhar GR (2006) Two regimens of twice-daily premix insulin analogue: an observational study. Diabetes Res Clin Pract 71:105-107.

43.Ciraldi TP, Phillips SA, Carter L, Aroda V, Mudaliar S, et al. (2005) Effect of the rapid-acting insulin analog glulisine on cultured human skeletal muscle cells: comparisons with insulin and insulin-like growth factor. J Clin Endocrinol Metab 90: 5551-5558.

44.Bixner DI, Marx CM (2008) Cost-effectiveness of insulin analogs. Am J managed Care14: 766-775.

45.Riddle M, Frias J, Zhang B, Maier H, Brown C, et al. (2007) Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. Diabetes Care 30: 2794-2799.

46.Davidson MB, Navar MD, Echeverry D, Duran P (2010) U-500 regular insulin. Diabetes Care 33: 281-283.

47.Nichol A, Chandra Sekar M (2011) Successful Management of Extremely Insulin-Resistant Obese Diabetic Patient with Insulin Glargine, U-500 Regular Insulin and Pramlintide. J Diabetes Metab 2:143.

48.Ramulu P, Giridharan NV, Udayasekhararao P, Janardanasarma MK (2011) Insulin Sensitization and Resistance Interrelationship in a Prediabetic Rat: A Quantitative Molecular Model. J Diabetes Metab 2:140.

49.Havele S, Dhaneshwar S (2010) Estimation of Metformin in Bulk Drug and in Formulation by HPTLC. J Nanomedic Nanotechnolo 1: 102.

50.Sharma RD (1986) Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses in human subjects. Nutr Res 6: 1353-1364.

51. Diabetes Association Diabetes Care 2018 Jan; 41(Supplement 1): S73-S85.

52.Trafton JA, Ramani A (2009) Methadone: A new old drug with promises and pitfalls. Curr Pain Headache Rep 13: 24-30.

53.Digby GC, Fong C, Methot MR, Simpson CS, Redfearn D, et al. (2011) Acquired QT Interval Prolongation & Methadone: The Risk of Pharmacological Interaction. J Clinic Experiment Cardiol 2:116.

54.Andrews CM, Krantz MJ, Wedam EF, Macuson MJ, Capacchione JF, et al. (2009) Methadone-induced mortality in the treatment of chronic pain: Role of QT prolongation. Cardiol J 16: 211-217.

55.Fouqueray P, Leverve X, Fontaine E, Baquié M, Wollheim C, et al. (2011) Imeglimin - A New Oral Anti-Diabetic that Targets the Three Key Defects of type 2 Diabetes. J Diabetes Metab 2:126.

56.Florez H, Scranton R, Farwell WR, DeFronzo RA, Ezrokhi M, et al. (2011) Randomized Clinical Trial Assessing the Efficacy and Safety of Bromocriptine-QR when Added to Ongoing Thiazolidinedione Therapy in Patients with Type 2 Diabetes Mellitus. J Diabetes Metab 2:142.

57.Mansour AA, Wanoose HL, Odaa AH (2011) A Three Year Cohort Prospective Type 2 Diabetes Control Study in Basrah. J Diabetes Metab 2:119.

58.Wright A, Burden AC, Paisey RB, Cull CA, Holman RR (2002) Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 25:330-336.

59.Shehata MF, Pater A (2011) Incretin-Based Therapies: What Do We Need To Know? J Diabetes Metab 2:146.

60.Kamoi K, Ohara N, Tomoo I, Shinozaki Y, Furukawa K (2011) Normal Response of Active GLP-1 like Substances Level to Test Meal in Non-Obese Type 2 Diabetic Japanese Patients with Complications and Receiving Treatments. J Diabetes Metab 2:147.

61.Dang Q, Reddy KR, Kasibthatla SR, Jiang T, Taplin F, et al. (2010) Discovery of Phosphonic Acid-Containing Desaminobenzimidazolesas Fructose 1,6-Bisphosphatase Inhibitors that are Suitable for Oral Delivery via Prodrugs. J Diabetes Metab 1:105.

62.Dang Q, Kasibhatla SR, Xiao W, Liu Y, Dare J, et al. (2010) Fructose-1,6-bisphosphatase Inhibitors. 2. Design, synthesis and structure-activity relationship of a series of phosphonic acid containing benzimidazoles that function as 5'-adenosinemonophosphate (AMP) mimics. J Med Chem 53: 441-451.

63.http://www.prokerala.com/health/ayurveda/diabetes-treatment.htm

64.Aggarwal N, Shishu (2011) A Review of Recent Investigations on Medicinal Herbs Possessing Anti-Diabetic Properties. J Nutrition Disorder Ther 1:102.

65.Poulose N, Vishnu Prasad CN, Nidhina Haridas PA, Anilkumar G (2011) Ellagic Acid Stimulates Glucose Transport in Adipocytes and Muscles through AMPK Mediated Pathway. J Diabetes Metab 2:149.

66.World Health Organization. *WHO Monographs on Selected Medicinal Plants*; World Health Organization: Geneva, Switzerland, 1999; Volume 1.

67.Farag, M.A.; Ali, S.E.; Hodaya, R.H.; El-Seedi, H.R.; Sultani, H.N.; Laub, A.; Eissa, T.F.; Abou-Zaid, F.O.F.; Wessjohann, L.A. Phytochemical profiles and antimicrobial activities of *Allium cepa* Red cv. and *A.*

sativum subjected to different drying methods: A comparative MS-based metabolomics. *Molecules* **2017**, *22*, 761.

68.Kim, S.-H.; Jo, S.-H.; Kwon, Y.-I.; Hwang, J.-K. Effects of Onion (*Allium cepa* L.) Extract Administration on Intestinal α-Glucosidases Activities and Spikes in Postprandial Blood Glucose Levels in SD Rats Model. *Int. J. Mol. Sci.* **2011**, *12*, 3757–3769.

69.Gautam, S.; Pal, S.; Maurya, R.; Srivastava, A.K. Ethanolic extract of *Allium cepa* stimulates glucose transporter typ 4-mediated glucose uptake by the activation of insulin signaling. *Planta Med.* **2015**, *81*, 208–214.

70.Kumari, K.; Augusti, K.T. Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (*Allium cepa* Linn) as compared to standard drugs in alloxan diabetic rats. *Indian J. Exp. Biol.* **2002**, *40*, 1005–1009.

71.Augusti, K.I.; Roy, V.C.; Semple, M. Effect of allyl propyl disulphide isolated from onion (*Allium cepa* L.) on glucose tolerance of alloxan diabetic rabbits. *Experientia* **1974**, *30*, 1119–1120.

72.World Health Organization. *WHO Monographs on Selected Medicinal Plants*; World Health Organization: Geneva, Switzerland, 2007; Volume 3.

73.Alzohairy, M.A. Therapeutics Role of *Azadirachta indica* (Neem) and Their Active Constituents in Diseases Prevention and Treatment. *Evid. Based Complement. Altern. Med.* **2016**, *2016*, 7382506.

74.Kumar, D.B.; Mitra, A.; Manjunatha, M. Azadirachtolide: An anti-diabetic and hypolipidemic effects from *Azadirachta indica* leaves. *Pharmacogn. Commun.* **2011**, *1*, 78–84.

75.Perez-Gutierrez, R.M.; Damian-Guzman, M. Meliacinolin: A potent alpha-glucosidase and alpha-amylase inhibitor isolated from *Azadirachta indica* leaves and in vivo antidiabetic property in streptozotocin-nicotinamide-induced type 2 diabetes in mice. *Biol. Pharm. Bull.* **2012**, *35*, 1516–1524.

76.World Health Organization. *WHO Monographs on Selected Medicinal Plants*; World Health Organization: Geneva, Switzerland, 2009; Volume 4.

77.Yuwai, K.E.; Rao, K.S.; Kaluwin, C.; Jones, G.P.; Rivett, D.E. Chemical composition of *Momordica charantia* L. fruits. *J. Agric. Food Chem.* **1991**, *39*, 1762–1763.

78.Chang, C.-I.; Tseng, H.-I.; Liao, Y.-W.; Yen, C.-H.; Chen, T.-M.; Lin, C.-C.; Cheng, H.-L. In vivo and in vitro studies to identify the hypoglycaemic constituents of *Momordica charantia* wild variant WB24. *Food Chem.* **2011**, *125*, 521–528.

79.Pattanayak, P.; Behera, P.; Das, D.; Panda, S.K. *Ocimum sanctum* Linn. A reservoir plant for therapeutic applications: An overview. *Pharmacogn. Rev.* **2010**, *4*, 95–105.

80.Murthy, H.N.; Dandin, V.S.; Lee, E.J.; Paek, K.Y. Efficacy of ginseng adventitious root extract on hyperglycemia in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* **2014**, *153*, 917–921.

81.World Health Organization. *WHO Monographs on Selected Medicinal Plants*; World Health Organization: Geneva, Switzerland, 2007; Volume 3.

82.Liu, C.; Ma, R.; Wang, L.; Zhu, R.; Liu, H.; Guo, Y.; Zhao, B.; Zhao, S.; Tang, J.; Li, Y.; et al. Rehmanniae Radix in osteoporosis: A review of traditional Chinese medicinal uses, phytochemistry, pharmacokinetics and pharmacology. *J. Ethnopharmacol.* **2017**, *198*, 351–362.

83. Koupy, D.; Kotolova, H.; Ruda Kucerova, J. Effectiveness of phytotherapy in supportive treatment of type 2 diabetes mellitus II. Fenugreek (*Trigonella foenum-graecum*). *Ceska Slov. Farm.* **2015**, *64*, 67–71.

84.Archer, A.W. Determination of cinnamaldehyde, coumarin and cinnamyl alcohol in cinnamon and cassia by high-performance liquid chromatography. *J. Chromatogr. A* **1988**, *447*, 272–276.

85.Ranasinghe, P.; Pigera, S.; Premakumara, G.A.S.; Galappaththy, P.; Constantine, G.R.; Katulanda, P. Medicinal properties of "true" cinnamon (*Cinnamomum zeylanicum*): A systematic review. *BMC Complement. Altern. Med.* **2013**, *13*, 275.

86.Biagi, M.; Pecorari, R.; Appendino, G.; Miraldi, E.; Magnano, A.R.; Governa, P.; Cettolin, G.; Giachetti, D. Herbal Products in Italy: The Thin Line between Phytotherapy, Nutrition and Parapharmaceuticals; A Normative Overview of the Fastest Growing Market in Europe. *Pharmaceuticals* **2016**, *9*, 65.