

A REVIEW ON COMPLICATION OF DIABETES MELLITUS AND ITS THERAPY**Brahm Kumar Tiwari^a, Bilal Ahmad Sheikh^b, A.B. Abidi^{a*}**^a*Department of Biochemistry & Biochemical Engineering, Sam Higginbottom Institute of Agriculture, Technology & Sciences, Allahabad. U.P.211007. India*^b*Vety. Biochemistry, faculty of Vety. Sciences & Animal Husbandry, Shere Kashmir University of Agricultural Sciences & Technology, Kashmir**Corresponding Author Email: profababidi@yahoo.in**ABSTRACT**

Diabetes is a grouping of anatomic and chemical problems resulting from a number of factors in which an absolute or relative deficiency of insulin and/or its function is present. It tends to run in Families; is associated with accelerated atherosclerosis, and predisposes to certain specific microvascular abnormalities including retinopathy, nephropathy and neuropathy. There are other problems, such as the lessening of resistance to infection, especially if the diabetes is poorly controlled. The objective of the present review is to provide an epidemiological, Experimental (alloxan, streptozotocin and other Drug induced diabetes) and available therapy; Insulin and other oral hypoglycemic Drugs generally used for therapy of diabetes have side effects. The review contains hyperglycemia increases reactive oxygen species (ROS) production and its effect. The review also contains Herbal plants which have been reported as antidiabetic, antioxidant and antihyperlipidemic activity. This review will also be helpful to researchers for understanding better possibilities about development of Alternative methods.

KEY WORDS*alloxan, Diabetes mellitus, herbal plant, oxidative stress, oral drugs, streptozotocin***INTRODUCTION**

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia arising as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action or both [1]. Nowadays more than 366 million people suffer from DM and 552 million are expected to be affected by diabetes by 2030 [2]. It is a group of metabolic disorder of endocrine system with various micro and macro vascular complications. It is characterized by high blood glucose levels (hyperglycemia) due to the inability of the body's cells to utilize glucose properly [3]. Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of populations in the world [4]. Diabetes mellitus is a disorder, characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin

action or both. Increased thirst, increase urinary output, ketonemia and ketouria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat and protein metabolism. When ketone bodies present in the blood or urine, it is called ketoacidosis, hence adequate treatment should be taken immediately, otherwise it can lead to other diabetic complications [5]. For the treatment of diabetes mellitus synthetic drugs are neither cheap nor completely effective. Furthermore, the long term consumption of synthetic drugs may cause adverse effects, while those medications provided from natural sources are more affordable and have shown lesser adverse effects [6].

EPIDEMIOLOGY OF DIABETES MELLITUS

The word 'diabetes' is derived from the Greek word "Diab" (meaning to pass through, referring to the

cycle of heavy thirst and frequent urination); 'mellitus' is the Latin word for "sweetened with honey" (presence of sugar in the urine). Greeks had a knowledge of a disease accompanied by polyurea and wasting of body, whereas Aretaeus of Cappadocia mentioned a disease characterized by thirst and polyurea which was christened as Diabetes. Subsequently, the knowledge spread to Chinese, Iranians and Arabians. From the Middle East, the knowledge of DM had spread to Spain as a disease characterized by polyurea, polydipsia with sugary flavoured urine. With discovery of sugar in urine and its detection by laboratory tests, the knowledge permitted into 18th century. Today, around 30 million people throughout the world suffer from DM. It is the most common metabolic abnormality in the world. Non-insulin dependent diabetes mellitus (NIDDM) is the most common form of diabetes constituting nearly 90% of the diabetic population in any country. Its prevalence varies in different geographic regions and also in different ethnic groups.

According to ancient Hindu physicians, 'Madhumeha' is a disease in which a patient passes sweet urine and exhibits sweetness all over the body, that is, Sweat, in mucus, breath, blood, etc. They knew of the fact that the urine of a Madhumeha patient tastes sweet [7].

The most populous countries of Asia-Pacific region in the world. The largest country, China, contains 20% of the world's population (1.2 billion). Asia also contains the world's second largest country, India, with a population of 1 billion and fourth largest country, Indonesia, with a population of about 200 million. Thus, the Asia-Pacific region is of prime importance to the epidemiology of diabetes. The region combines a high proportion the world's population with rapidly rising diabetes prevalence rates. The Western Pacific region, along with the Indian subcontinent, is at the forefront of the current epidemic of type 2 diabetes mellitus. In 1998 it was estimated that, globally, there were already 140 million people with diabetes. Predictions compiled by Dr Hilary King of the World Health Organization (WHO) report the figure will rise to 300 million by the year 2025. Of these, more than 150 million will be in Asia. India are predicted to rise from an estimated 15 million in 1995 to 57 million in 2025. For China, current estimates are 15 to 20 million, with a predicted rise to 50 million by 2025.

Thus, more than 30% of the global number of people with diabetes in 2025 will be in these two countries alone [8].

TYPE OF DIABETES MELLITUS

Diabetes mellitus can be divided in to two main types, Type 1, "Juvenile Diabetes mellitus" (Insulin Dependent Diabetes Mellitus, IDDM), and Type 2, "Adult type" (Non-Insulin Dependent Diabetes Mellitus, NIDDM) [7], Type 1 diabetes mellitus is characterized by a deficiency in endogenous insulin production mediated by an autoimmune process destroying the insulin-producing beta cells of the endocrine pancreas resulting in a dependency of exogenous insulin injections [9]. This is the result of The combination of genetic susceptibility along with environmental factors [10]. Type 2, diabetes is generally viewed as a clinical syndrome with variable phenotypic expression rather than a single disease with a specific etiology. Phenotypic elements of the syndrome include cell insufficiency and insulin resistance. However, in most instances, the exact cause of type 2 diabetes seems to be polygenic in nature and is as yet unknown.

Regardless of the primary causes of type 2 diabetes, a common clinical course is for patients to respond to therapy initially by normalizing their fasting glucose levels, but then to undergo gradual deterioration in glycemic control despite optimal medical management using a variety of drugs [11]. Other type of diabetes is gestational diabetes which is mainly associated with pregnancy. Genetic defects of β - cells function or insulin action is also a type of diabetes mellitus commonly called maturity onset diabetes [5]. Neonatal diabetes mellitus is also a type of disorder in which insulin is required for the maintenance of blood glucose level in the first three months of life. It may be associated with intrauterine growth retardation and defects of chromosomes [5]. Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterised by progressive non-autoimmune β cell failure [5]. Diabetes related to Cystic fibrosis is primarily due to insulin deficiency, but insulin resistance during acute illness, secondary to infections and medications, may also contribute to impaired glucose tolerance and diabetes. Sometimes

diabetes can also occur by other factors. Like stress or in other case by the use of medication such as dexamethasone, L- asparaginase, glucocorticoids, cyclosporine or tacrolimus, olanzapine, risperidol, quetiapine and ziprasidone [5].

CAUSE OF DIABETES MELLITUS

The causes of diabetes depend on the type of diabetes. Type 1 occurs mainly due to β - cell destruction, mediated through either immune mediated or idiopathic, whereas Type 2 diabetes occurs mainly due to insulin resistance or with relative insulin deficiency. Diabetes is also associated with life style factors and genetics [5]. There are various types of other factors involved in the development of diabetes which are the genetic material such as chromosomal and mitochondrial DNA mutation, Leprechaunism, Rabsonmendenhall syndrome and lipoatrophic diabetes is associated with the genetic defects in insulin action. In some cases congenital rubella and cytomegalovirus infection also lead to the cause of diabetes mellitus. Sometimes drugs and other chemicals such as pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, β -adrenergic agonists, thiazides, α - interferon can cause diabetes mellitus. Abnormalities such as pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, fibrocalculus, pancreatopathy can also develop diabetes. There are other factors related to immune system such as 'Stiff- man' syndrome and anti-insulin receptor antibodies that are involved in the development of the diabetes.

Disease associated with pancreas such as acromegaly, cushing's syndrome, glucagonoma, pheochromocytomas, hyperthyroidism and aldosteronoma can also mediate diabetes mellitus. There are some other genetic syndromes such as Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram, Friedreich's ataxia, Huntington's chorea, Laurence- Moon- Biedl syndrome, Myotonic dystrophy, Prader -Willi syndrome which were also involved in the development of diabetes in some cases [5].

CORRELATION BETWEEN OXIDATIVE STRESS AND DIABETES MELLITUS

In physiologic concentrations, endogenous reactive oxygen species (ROS) help to maintain homeostasis. However, when ROS accumulate in excess for prolonged periods of time, they cause chronic oxidative stress and adverse effects. This is particularly relevant and dangerous for the islet, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses. Multiple biochemical pathways and mechanisms of action have been implicated in the deleterious effects of chronic hyperglycemia and oxidative stress on the function of vascular, retinal, and renal tissues. Considerably less work has been performed using islet tissue [12]. Hyperglycemia can increase oxidative stress and change the redox potential of glutathione and whereby reactive oxygen species can cause hyperglycemia [3].

DIAGNOSIS OF DIABETES MELLITUS

Elevated blood glucose level and the presence and absence of symptoms such as polyuria, polydipsia, fatigueness, blurring of vision and weight loss in association with glycosuria and ketouria are the main diagnostic criteria of diabetes. Diabetes mellitus can be confirmed by measurement of a marked elevation of the blood glucose level. The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting or 2 hour post-prandial blood glucose levels and an oral glucose tolerance test (OGTT). Symptoms of diabetes plus plasma glucose concentration ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl and 2-hours post load glucose ≥ 200 mg/dl during an OGTT were considered as diabetes [7, 5].

Sometimes measurement of specific antibody markers such as islet cell antibody (ICA), GAD, IA₂, IAA and HbA_{1c} may be helpful for the diagnosis of diabetes mellitus. Measurement of fasting insulin and C- peptide level can also be useful in the diagnosis of type 2 diabetes in children [5].

EXPERIMENTAL MODELS FOR DIABETES MELLITUS

The various experimental models developed for studying diabetes mellitus, assess the merits and

demerits of each model. The currently existing animal models include:

Normoglycaemic animal model

Normal healthy animals can be used for testing potential oral hypoglycaemic agents. This is still a valid screening method which is often used in addition to diabetic animal models. This method allows for the effect of the drug to be tested in the animal with an intact pancreatic activity. The comparison may give some information regarding mechanism of action. Hyperglycaemic agent may be detected at the same time [13].

Chemical induction of diabetes mellitus

The majority of studies for diabetes employed this model. Streptozotocin (STZ) and alloxan are toxic glucose analogues most frequently used drugs and this model has been useful for the study of multiple aspects of the disease. Both drugs exert their diabetogenic action when they are administered parenterally (intravenously, intraperitoneally or subcutaneously). The dose of these agents required for inducing diabetes depends on the animal species, route of administration and nutritional status [14].

Streptozotocin

Streptozotocin (2-Deoxy-2-((methylnitrosoamino) carbonyl) amino)-D-glucopyranose) inhibits insulin secretion and causes a state of insulin-dependent diabetes mellitus. Both effects can be attributed to its specific chemical properties, namely its alkylating potency. As with alloxan, its beta cell specificity is mainly the result of selective cellular uptake and accumulation [15]. Diabetes induced by an injection of a single intraperitoneal dose of streptozotocin (65 mg/kg). Rats with Fasting blood glucose ≥ 200 mg/dl but ≤ 500 mg/dl were included in the study [16]. Diabetes was induced in overnight fasted male Wistar rats by a single intraperitoneal injection (i.p.) of freshly prepared solution of streptozotocin (50 mg/kg body weight) in 0.1 M citrate buffer (pH 4.5). The animals were confirmed diabetic by the elevated plasma glucose levels after 72 h of injection [17].

Alloxan

Alloxan (2,4,5,6-Tetraoxypyrimidine; 2,4,5,6-pyrimidinetetrone) has two distinct pathological effects: it selectively inhibits glucose-induced insulin secretion through specific inhibition of glucokinase,

the glucose sensor of the beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce ROS formation, resulting in the selective necrosis of beta cells. These two effects can be assigned to the specific chemical properties of alloxan, the common denominator being selective cellular uptake and accumulation of alloxan by the beta cell. Alloxan is a very unstable chemical compound with a molecular shape resembling glucose [15]. Diabetes was induced in experimental rats by single intraperitoneal injection of alloxan (120 mg/kg body weight). Blood glucose levels of 300 mg/dl or more were considered diabetic [18]. The rats were injected with alloxan monohydrate dissolved in sterile normal saline at a dose of 150 mg/kg bodywt. intraperitoneally. After 2 weeks, rats with moderate diabetes having glycosuria indicated by uristrips and hyperglycaemia i.e. with a blood glucose of 200-260 mg/dl. were used for the experiment [19]. Diabetes mellitus was induced in the rats by single intraperitoneal injection of 160 mg/kg b.w. of freshly prepared alloxan monohydrate in normal saline. In order to prevent fatal hypoglycaemia due to massive pancreatic insulin release, rats were treated with 20% glucose solution intraperitoneally after 6 h followed by 5% glucose solution bottles in their cages for a period of 24 h. After one wk, the animals showing blood glucose level >13.8 mmol/l were considered diabetic and used for the study [20].

Ferric nitrilotriacetate induction of diabetes mellitus

This is a rarely used procedure. Rats and rabbits parenterally treated with a large daily dose of ferric nitrilotriacetate manifested diabetic symptoms such as hyperglycaemia, glycosuria, ketonemia and ketonuria after approximately 60 days of treatment. The blood insulin response to oral glucose loading was poor [21]. Induction of diabetes mellitus with ditizona or anti – insulin serum has never been reported.

Surgical model of diabetes mellitus

Another technique used to induce diabetes is complete removal of the pancreas (pancreatectomy). Few researchers have employed this model in the last years to explore effects of natural products with animal species such as rats, pigs, dogs and primates [22-24]. Limitation to this technique include high level of technical expertise and adequate surgical room

environment, major surgery and high risk of animal infection, adequate post-operative analgesia and antibiotic administration, supplementation with pancreatic enzymes to prevent malabsorption and loss of pancreatic counter regulatory response to hypoglycemia. More recently, partial pancreatectomy has been employed, but large resection (more than 80% in rats) is required to obtain mild to moderate hyperglycemia. In this case, small additional resection can result in significant hypoinsulinemia [24]. Choi investigated the action of relative glucose uptake in various tissues of 90% pancreatectomized rats by using either hyperglycemic or euglycemic hyperinsulinemic clamp methodologies. This experimental design permits to evaluate if the compound has some effect upon both resistance and secretion of insulin [22].

THERAPY FOR DIABETES MELLITUS

The treatment of diabetes mellitus is considered as the main global problem and successful treatment has yet to be discovered. Even though insulin therapy and oral hypoglycemic agents are the first line of treatment for the diabetes mellitus they have some side effect and fail to significantly alter the course of diabetic complications [25].

Human insulin

Human insulin is a polypeptide, having a molecular weight of about 6000 Da, consisted of two amino acid chains A and B, which are linked by two disulphide (-S-S-) linkage. Normal human pancreas contains about 8-10 mg. of insulin. Insulin is not suitable for oral administration due to inactivation by digestive enzyme. 80% of excreted insulin is normally degraded in the liver and kidneys. The amount of insulin secreted per day in a normal human is about 40 units. The dose of insulin required to control the diabetes varies from patient to patient and from time to time in the same patient [7].

Oral hypoglycaemic drugs

Oral hypoglycemic drugs are used only in the treatment of type 2 diabetes which is a disorder involving resistance to secreted insulin. Type 1 diabetes involves a lack of insulin and requires insulin

for treatment. There are now four classes of hypoglycemic drugs:

Sulfonylureas

Metformin

Thiazolidinediones

Alpha-glucosidase inhibitors.

Sulfonylureas

Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes and appear to function by stimulating insulin secretion. The net effect is increased responsiveness of β -cells (insulin secreting cells located in the pancreas) to both glucose and non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal. Sulfonylureas are usually well tolerated. Hypoglycemia is the most common side effect and is more common with long-acting sulfonylureas [26].

Repaglinide

Repaglinide is a short-acting glucose-lowering drug recently approved by the Food and Drug Administration for therapy of type 2 diabetes alone or in combination with metformin. It is structurally different than sulfonylureas, but acts similarly by increasing insulin secretion [26].

Natiglinide

Natiglinide (Starlix) is a very short-acting glucose lowering drug whose mode of action is similar to the sulfonylureas and is nearing approval by the FDA. A potential advantage of this drug is that it seems to have its effect on the first phase of insulin release rather than the late phase of insulin release. The first phase of insulin release is brisk, of short duration and occurs within minutes of ingesting food. It is this first phase of insulin release that is abnormal in early diabetes & can often be found in patients with impaired glucose tolerance prior to the onset of diabetes. The usual dose is 120 mg before meals [26].

Metformin

Metformin has been used in Europe for over thirty years, and has been available in the United States since March 1995. It is effective only in the presence of insulin but, in contrast to sulfonylureas, it does not

directly stimulate insulin secretion. Its major effect is to increase insulin action.

How metformin increases insulin action is not known but it is known to affect many tissues. One important effect appears to be suppression of glucose output from the liver. The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and diarrhea. These symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug [26].

Thiazolidinediones

The thiazolidinediones such as Avandia (Rosiglitazone) and Actos (Pioglitazone) reverse insulin resistance by acting on muscle, fat and to a lesser extent liver to increase glucose utilization and diminish glucose production.

The mechanism by which the thiazolidinediones increase insulin action is not well understood but they may be acting by redistributing fat from the visceral compartment to the subcutaneous compartment. We know that visceral fat is associated with insulin resistance [26].

Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitors include acarbose (Precose) & Miglitol (Glycet) and are available in the United States. They inhibit the upper gastrointestinal enzymes that converts dietary starch and other complex carbohydrates into simple sugars which can be absorbed. The result is to slow the absorption of glucose after meals.

As in patients with type 2 diabetes, patients with type 1 diabetes have a reduction in the amplitude of glucose excursion and HbA1c and a possible reduction in nocturnal hypoglycemia with alpha-glucosidase inhibitors.

The main side effects of alpha-glucosidase inhibitors are flatulence and diarrhea. These symptoms are usually mild and do not necessitate cessation of therapy [26].

HERBAL TREATMENT FOR DIABETES MELLITUS

In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Sushruta. Plants have always been an

exemplary source of drugs and many of the currently available drugs have been derived directly and indirectly from them. The ethnobotanical information report that about 800 plants may possess anti-diabetic potential [27].

Azadirachta Indica

Azadirachta Indica (AI) has hypoglycaemic action in its leaves, stem and bark and seed oils as well as other medicinal uses of AI and pharmacologically reported biological actions have been articulated in a review by Biswas [28].

Murraya Koenigii

The leaf extract of *M. koenigii* significantly decreased the level of blood glucose in experimental diabetic rats [29] and carbazoles from *M. koenigii* leaf extract have strong antioxidative activity [30,31].

Ocimum Sanctum

Leaves of *Ocimum sanctum* Linn (*O. sanctum*), commonly known as Tulsi are similarly studied for their hypoglycaemic and antioxidative properties; it is shown to decrease blood glucose level in alloxan diabetic rats [32] but, most significant is the ability of Tulsi leaf extract to reduce lipid peroxidation and glutathione levels in Wistar rats [33].

Aegel Marmelose

Antidiabetic properties of *A. Marmelos* leaf extract in glucose-induced hyperglycemia [34] and alloxan-induced diabetes [35] have been reported.

Syzigium Cumini

Syzigium cumini possess a range of pharmacological properties such as antibacterial, antifungal, antiviral, anti-genotoxic, anti-inflammatory, anti-ulcerogenic, cardioprotective, anti-allergic, anticancer, chemopreventive, radioprotective, free radical scavenging, antioxidant, hepatoprotective, anti-diarrheal, hypoglycemic and antidiabetic effects [36].

Terminalia chebula Retz.

Terminalia chebula Retz. has been widely used in diabetes in Ayurveda and is widely distributed in India. An herbal formulation containing *T. chebula* named TRIPHALA is traditional medicine for the treatment of diabetes. Antidiabetic and renoprotective effects of the chloroform extract of *T. chebula* Retz seeds in streptozotocin-induced diabetic rats was proved. It has potent renoprotective action [37].

Momordica charantia

Momordica charantia is commonly used as an antidiabetic Anticancer, antiinflammation, antiviral, antioxidant, antimutagen and cholesterol lowering agent in India as well as other Asian countries [38]. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of M. charantia showed significant hypoglycemic effect when administered subcutaneously to langurs and humans [39].

Tinospora cordifolia

It is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of Tinospora cordifolia (T.cordifolia) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight [40].

Aloe vera Linn

Bioactive compounds from aloe vera are very effective in various treatments, such as Diabetes, burns, allergic reactions, rheumatoid arthritis, rheumatic fever, acid indigestion, ulcers, skin diseases, dysentery, diarrhoea, piles and inflammatory conditions of the digestive system and other internal organs, including the stomach, small intestine, liver, kidney, and pancreas. The active ingredients have been shown to have analgesic, anti-inflammatory, antioxidant and anticancer agent [41].

Gymnema montanum Hook.f.

G.montanum (Madhunasni)ethanolic leaf extract possess antihyperglycemic and antiperoxidative effect. It has been reported to be rich in gymnemagenin and gymnemic acids that are responsible for antihyperglycemic effect [42]. The decrease in lipid peroxides, increase in reduced glutathione, ascorbic acid (vitamin C) and a-tocopherol (vitamin E). In the study by Ananthan et al. has shown treatment of diabetic rats with leaf extract increased the antioxidant levels [43].

Andrographis paniculata

Andrographis paniculata has a broad range of pharmacology effects such as antidiabetic, anti-inflammatory, antidiarrhoeal, cardiovascular, anticancer and immune stimulatory activities [44].

Coccinia indica

Coccinia indica is famous plant for its safe antidiabetic property. It is proved the insulin stimulatory effect of C. indica leaves from existing b-cells in diabetic rats. It possesses hypoglycemic, antidiabetic, hypolipidemic, hepatoprotective, larvicidal, Anti-inflammatory, analgesic and antipyretic activities. It is found to devoid of antituberculosis properties [45].

Tinospora Cordifolia (Gaduchi)

Tinospora cordifolia is a widely used shrub in folk and ayurvedic systems of medicine. The notable medicinal properties reported are anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities [46].

Mucuna pruriens Linn.

Mucuna pruriens Linn. Commonly used for the management of several free radical-mediated diseases such as diabetes, ageing, rheumatoid arthritis, atherosclerosis, male infertility and nervous disorders. It is also used as an aphrodisiac and in the management of Parkinsonism [47, 48].

Achyranthes aspera

Achyranthes aspera plant possesses activities like antidiabetic antiperiodic, diuretic, purgative, laxative, antiasthmatic, hepatoprotective, anti-allergic and various other important medicinal properties [49,50].

Caesalpinia bonducella

Caesalpinia bonducella posses multiple therapeutic properties like antidiabetic, antipyretic, antidiuretic, anthelmintic and antibacterial, anticon-vulsant, anti-anaphylactic and antidiarrheal, anti-viral, antiasthmatic, antiamebic, antiestrogenic, hepatoprotective and antioxidant properties [51,52].

Phyllanthus niruri Linn

The whole plant is used as remedies for many conditions such as Diabetes dysentery, influenza, vaginitis, tumours, diuretics, jaundice, kidney stones and dyspepsia. The plant is also useful for treating hepatotoxicity, hepatitis B, hyperglycaemia and viral and bacterial diseases [53].

Saraca Indica

Saraca Indica plant useful in treatment of Diabetes Mellitus, Uterine stimulant, sedative, oxytocic activity, In menorrhagia Non Phenolic glycoside has Parasympathomimetic activity. In intrinsic

hemorrhages Ashoka flower are used. Used in burning sensation. Dried flowers used in Diabetes [54].

Emblca officinalis

Emblca officinalis (Amla) are widely used in the Indian system of medicine and believed to increase defense against cancer, diabetes, liver treatment, heart disease, ulcer, anemia, antioxidant, immunomodulatory, antipyretic, analgesic, cytoprotective, antitussive and gastroprotective effect [55].

Gymnema sylvestre

Gymnema sylvestre is used in the treatment of diabetes mellitus and in food additives against obesity and caries anti-allergic, antiviral, lipid lowering and antioxidant effect [56].

Enicostemma littorale

Enicostemma littorale used in the treatment of diabetes and also has antioxidant activity [57].

Psoralea corylifolia

Psoralea corylifolia has significant anti-hyperglycemic and antioxidant activity. It influences antioxidant parameter like decrease malondialdehyde (MDA) level and increase reduced glutathione (GSH) level [58].

Holarrhena antidysenterica

In Indian traditional medicine, the plant has been considered a popular remedy for the treatment of dysentery, diarrhea, intestinal worms, antidiabetic and antihyperlipidemic activity [59,60].

Artocarpus heterophyllus

Many parts of the plant including the bark, roots, leaves, and fruit are attributed with medicinal properties. It is reported in Ayurveda (a traditional medicine system in Sri Lanka and India) to possess antibacterial, anti-inflammatory, antidiabetic, antioxidant and immunomodulatory properties [61].

COMPOSITE FORMULATION OF HERBAL PLANTS

In the traditional system of Indian medicine, plant formulation and combined extracts of plants are used as drug of choice rather than individual. Some study revealed the better effect of composite formulation in treatment of diabetes. Diasulin, a combination of ten herbal plants exert a significant antihyperlipidemic and antiperoxidative effect. This could be due to different types of active principles, each with a single

or a diverse range of biological activities, which serves as a good adjuvant in the present armamentarium of antidiabetic drug [62] Dihar is a combination of 8 herbal medicinal plants exerts a significant antidiabetic, antihyperlipidemic and antioxidant effect. This could be due to different type of active principles from various plants, which may have different mechanisms of action therefore combination may be beneficial [63].

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