



Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd

Document heading

doi:10.1016/S2222-1808(14)60585-5

© 2014 by the Asian Pacific Journal of Tropical Disease. All rights reserved.

Diabetes mellitus and medicinal plants—a review

Surenran Surya, Abdul Dhaliya Salam, Dawn Vallikattukuzhiyil Tomy, Betty Carla, Ravindrakurup Arun Kumar, Christudas Sunil*

St. Joseph College of Pharmacy, Cherthala, Kerala, India

PEER REVIEW

Peer reviewer

Dr. C. T. Kumarappan, Ph.D., Senior Lecturer, School of Pharmacy, Faculty of Medicine and Health Sciences, Taylor's University (Lakeside Campus), No: 1 Jalan Taylor's, Subang Jaya, Selangor D.E, 47500, Malaysia.
Tel: +03 56295000;
Fax: 03 56295001
E-mail: ctkumarrx@gmail.com

Comments

This is a good review paper in which the authors have reviewed about DM and the role of medicinal plants for the treatment. I recommend this article to be published.

Details on Page 344

ABSTRACT

Diabetes mellitus is a group of metabolic disorders sharing the common underlying feature of hyperglycemia. Along with hyperglycemia, diabetes is associated with micro and macro-vascular complications, which are the major causes of morbidity and death in diabetic subjects. The currently available antidiabetic agents include sulfonylureas, biguanides, thiazolidinediones and alpha glucosidase inhibitors and are widely used to control the hyperglycemia. These drugs fail significantly to alter the course of diabetic complications. They have limited use because of undesirable pathological conditions and high rates of secondary failure. Thus, it is essential to look for more effective antidiabetic agents with fewer side effects. Traditional medicinal plants having antidiabetic properties can be a useful source for the development of safer and effective oral hypoglycemic agents. More than 350 traditional plants are used in the treatment of diabetes mellitus, which have been recorded. Only a small number of these have received scientific and medical evaluation to assess their efficacy. However, plant remedies are the mainstream of treatment in underdeveloped regions. This review focuses on diabetes mellitus and the role of plants in the treatment of diabetes mellitus.

KEYWORDS

Diabetes mellitus, Hyperglycemia, Medicinal plants, Insulin

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder, resulting from insulin deficiency, characterized by abnormal increase in the blood sugar level, altered metabolism of carbohydrates, protein and lipids, and an increased risk of vascular complications^[1,2]. Uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis leads to hyperglycemia^[3]. Long term damage and failure of different organs were found along with chronic

hyperglycemia^[2].

As per World Health Organization, DM is a chronic metabolic disorder characterized by common features of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism^[4]. There are numerous pathogenic processes involved in the development of diabetes. This includes autoimmune destruction of the β -cells of the pancreas which leads to consequent insulin deficiency and abnormalities that result in resistance to insulin action. Deficiency of insulin on target tissues causes abnormalities in carbohydrate, fat, and protein

*Corresponding author: Dr. Christudas Sunil, Head of the Department of Pharmacology, St. Joseph College of Pharmacy, Cherthala, Kerala, India.

Tel: +91 9791442207

E-mail: sunilology@yahoo.co.in

Foundation Project: Supported by Indian Council of Medical Research, New Delhi for providing Senior Research Fellowship (Grant No. 45/31/2010/BMS/TRM)

Article history:

Received 15 May 2014

Received in revised form 17 May, 2nd revised form 30 May, 3rd revised form 1 Jun 2014

Accepted 13 Jun 2014

Available online 2 Jul 2014

metabolism. It may be due to inadequate insulin secretion and/or diminished tissue responses to insulin[1,2].

Signs and symptoms of hyperglycemia include polyuria, polydipsia, weight loss, polyphagia, blurred vision, tachycardia, hypotension and wasting[1–5]. Chronic hyperglycemia may also cause impairment of growth, susceptibility to certain infections[2]. Uncontrolled diabetes causes ketoacidosis of different grades and hyperosmolar (nonketotic hyperglycemic) coma. Its cause is obscure but appears to be precipitated by the same factors as ketoacidosis especially those resulting in dehydration[6]. The development of foot ulcer, renal impairment and retinopathy may be considered as long term complications of long-standing diabetes in a patient[7]. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, cerebrovascular, peripheral and arterial diseases[2]. Hypertension often coexist with diabetes, promoting progressive renal damage[8]. Abnormalities of lipoprotein metabolism are often found in people with diabetes[1].

2. Epidemiology

As of 2010, an estimated 280 million people had diabetes, with type 2 making up about 90% of the cases globally[9]. The incidence of this disease is increasing rapidly and at the end of 2030, the number of cases will be double, as a result of increasing longevity and obesity. Diabetes is more common in developed countries, even though there is an increase in the prevalence rate in Asia and Africa. Environmental and genetic factors play an important role in the development of diabetes in varying populations[10].

The incidence of insulin dependent DM ranged from 1.8 to 7.0/100 000 per year in Africa, 0.14 to 10/100 000 per year in Asia, approximately 3.4 to 36/100 000 per year in Europe, 2.61 to 20.18/100 000 per year in the Middle East and 7.60 to 25.6/100 000 per year in North America and that of non insulin dependent DM ranged from 0.4% to 17.9% in Africa, 1.2% to 14.6% in Asia, 0.7% to 11.6% in Europe, 5.6% to 40% in the Middle East and 7% to 28.2% in North America[11].

3. Etiologic classification of DM

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class[2]. According to American Diabetes

Association[2], diabetes has been classified (Table 1).

Table 1

Classification of diabetes mellitus.

No.	Type	Symptom
I	Type 1	β-cell destruction, usually leading to absolute insulin deficiency A. Immune mediated B. Idiopathic
II	Type 2	Insulin resistance with relative insulin deficiency
III	Other specific types	1. Chromosome 12, HNF-1α (MODY3) 2. Chromosome 7, glucokinase (MODY2) 3. Chromosome 20, HNF-4α (MODY1) 4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4) 5. Chromosome 17, HNF-1β (MODY5) 6. Chromosome 2, NeuroD1 (MODY6) 7. Mitochondrial DNA A. Genetic defects of β-cell function 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome B. Genetic defects in insulin action 1. Pancreatitis 2. Trauma/pancreatectomy 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalculous pancreatopathy C. Diseases of the exocrine pancreas 1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Others D. Endocrinopathies 1. Vacor 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormone 6. Diazoxide 7. β-adrenergic agonists 8. Thiazides 9. Dilantin 10. γ-Interferon 11. Others E. Drug or chemical induced 1. Congenital rubella 2. Cytomegalovirus 3. Others F. Infections 1. "Stiff-man" syndrome 2. Anti-insulin receptor antibodies 3. Others G. Uncommon forms of immune-mediated diabetes 1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Friedreich ataxia 6. Laurence-Moon-Biedl syndrome 7. Prader-Willi syndrome H. Other genetic syndromes sometimes associated with diabetes
IV	Gestational diabetes mellitus[12]	–

4. Pathophysiology of DM

The pathophysiology of diabetes depends on knowledge of the basics of carbohydrate metabolism and insulin action. Carbohydrates from the food are broken down into glucose molecules in the gut and this glucose is absorbed into the bloodstream, elevating the blood glucose levels which results in the secretion of insulin from the pancreatic beta cells. Insulin binding to specific cellular receptors facilitates entry of glucose into the cell. The cell uses glucose for energy production. The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowered of blood glucose levels. Lower glucose levels in turn results in decreased insulin secretion. If insulin production and secretion are altered by diseases, blood glucose dynamics will also change. The decrease in insulin production may inhibit glucose entry into the cells resulting in hyperglycemia. Inadequate utilization of pancreatic insulin by the cells also leads to abnormal increase in the blood sugar level. When there is an elevation in the insulin secretion, blood glucose level becomes low (hypoglycemia) as large amounts of glucose enters the cells and little remains in the bloodstream^[13].

Excess glucose is stored in the liver and muscles as glycogen. Later, when energy is needed, glycogenolysis converts stored glycogen back to glucose. Triglycerides also formed from excess glucose and stored in adipose tissue which may subsequently undergo lipolysis, yielding glycerol and free fatty acids. The liver also produces glucose from

proteins and fat through a process called gluconeogenesis. Normal homeostasis is achieved through a balance of the metabolism of glucose, free fatty acids and amino acids, which maintains a blood glucose level, sufficient to provide an uninterrupted supply of glucose to the brain^[14]. The counter-regulatory hormones such as glucagon, catecholamines, growth hormones, thyroid hormones and glucocorticoids also affect the normal blood glucose level (Figure 1)^[15].

4.1. Type 1 DM

Type 1 diabetes most commonly develop in childhood and progresses with age. It is called as insulin dependent DM^[16,17]. The basic phenomena in the type 1 diabetes is cell-mediated autoimmune destruction of pancreatic beta islet cells. This leads to absolute insulin deficiency and predisposes the individuals to diabetic ketoacidosis (DKA) ^[18]. Type 1 diabetes is autoimmune in nature, although idiopathic destruction of beta cells which has a tendency to develop ketosis also comes under this group. All the patients with type 1 DM need insulin as a therapeutic agent.

Destruction of beta cells and insulin deficiency in a genetically predisposed individual arise from the environmental factors which triggers an autoimmune process is a main feature of type 1 diabetic patients^[16]. Several mechanisms contribute to beta cell destruction^[19]. T lymphocytes react against beta cell antigens and cause cell damage. The islets show cellular necrosis and lymphocytic infiltration. The lesion is called as insulinitis and locally

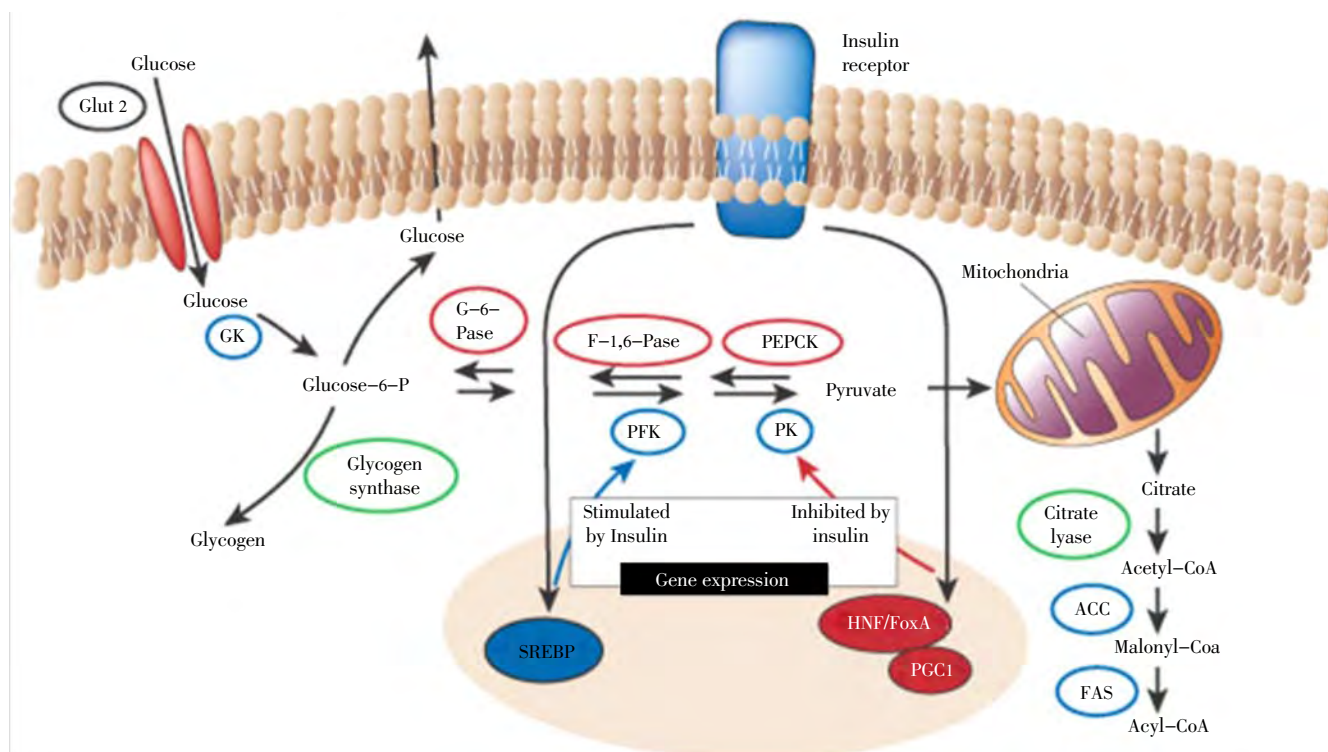


Figure 1. Mechanism of action of insulin.

produced cytokines can damage beta cells^[20].

Genetic and environmental modifiers causes dysregulation of the immune system and this will lead to the formation of auto antibodies^[16]. These antibodies may involve in causing the disease or it may be a result of T-cell mediated cell injury and release of normally sequestered antigens^[21]. Autoimmune disorders found with type 1 DM are Graves' disease, pernicious anaemia *etc.* in about 10%–20% cases^[22]. Auto antibodies may be found in some patients, even 15 years before the onset of acute disease. This could eventually provide a means of early identification of prediabetics so that they may be treated prophylactically, possibly by immunotherapy^[23].

The presence of genetic component in type 1 diabetes involves the inheritance of multiple genes to confer susceptibility to the disorder^[18]. Diabetes has a complex pattern of genetic associations, and the susceptibility genes have been mapped to at least 20 loci^[24]. In a human leukocyte antigen–associate susceptible individual, beta cells act as autoantigens and activate CD4⁺ T lymphocytes, bringing about immune destruction of pancreatic beta cells^[18].

The environmental factors play an important role in the pathogenesis of type 1 DM^[25]. There is an existence of the environmental modifiers of the disease^[16]. Epidemiologic studies suggest the role of viruses, experimental induction with certain chemicals such as alloxan, streptozotocin, early life factors, vaccinations *etc.* Recently, it is thought that environmental agents serve as modifiers of genetic susceptibility to autoimmunity^[16,26].

4.2. Type 2 DM

Type 2 DM previously called non insulin dependent DM or maturity–onset diabetes. It has a late onset and this type comprises about 90% of all cases of diabetes. The two metabolic defects that characterize type 2 diabetes are insulin resistance and inadequate insulin secretion. Type 2 DM is a heterogenous disorder with more complex etiology and is far more common than type 1, but less much known about its pathogenesis^[27]. It is characterized by a slow, gradual onset of hyperglycemia that is often asymptomatic. Elevation in the blood glucose levels results from increasing insulin resistance and impaired insulin secretion leading to relative insulin deficiency. Genetic defects, heredity and certain environmental factors play key role in the development of the disease^[28].

4.2.1. Genetics

Multifactorial inheritance is the most important factor in the development of type 2 DM^[27]. Genetic defects of insulin signaling pathway and insulin receptor mediates insulin resistance. Children of type 2 patients show the signs of insulin resistance at an early age. Specific point mutation accounts only for a minority (less than 5%) of patients with

the insulin resistance^[29]. Analysis of candidate genes have yielded many polymorphisms that associate with type 2 diabetic phenotype, but in most cases the associations have been weak, or the studies were not reproducible^[30].

4.2.2. Environment

Environmental factors which specifically targets beta cell, triggers the autoimmune process^[16].

4.2.3. Beta cell dysfunction

Failures of beta cell function leads to inadequate secretion of insulin, the exact genetic mechanism behind the fall in secretion in these cases are unclear. The possibilities involves amylin which forms fibrillar protein deposits in pancreatic islets, glucose toxicity and lipotoxicity in these cases may worsen the islet cell function^[31].

4.2.4. Insulin resistance

Insulin resistance is defined as resistance to the effects of insulin on glucose uptake, metabolism or storage^[32]. Genetic defects in insulin signaling pathway are not common and if present, are more likely polymorphisms with subtle effects rather than inactivating mutations^[33]. The acquired causes of insulin resistance involves nutrition, physical activity and obesity and these are closely associated with each other^[16].

4.2.5. Obesity

The link between obesity and diabetes is mediated via effects on insulin resistance^[34].

4.2.6. Role of free fatty acids

Excess circulating free fatty acids are deposited in the muscle and liver tissues of obese individuals leading to an increase in the level of intracellular triglycerides. These triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state. A decrease in activity of key insulin–signaling proteins mediates the lipotoxic effects of free fatty acids^[35].

4.2.7. Role of adipokines

A variety of proteins released into the systemic circulation by adipose tissue have been identified. Dysregulation of adipokine secretion may be one of the mechanisms by which insulin resistance is tied to obesity^[36].

4.2.8. Nutrition

Nutrition plays an important role in the development of obesity, insulin resistance and type 2 diabetes. Increase in the total caloric intake leads to obesity^[37].

4.2.9. Physical activity

Physical activity is one of the principal therapies to acutely lower blood glucose in type 2 diabetes due to its synergistic action with insulin in insulin–sensitive tissues^[38]. Essential

hypertension is a common risk factor in patient with type 2 DM. Some studies shows tht regular physical activity lower blood pressure in person with type 2 DM[39,40]. Weight loss leads to decrease in insulin resistance which may be most beneficial early in progression of the disease[41].

5. Diagnosis of diabetes and prediabetes

Blood tests are used in the diagnosis of diabetes and prediabetes. Type 2 diabetes may have no symptoms. Currently, the American Diabetes Association recommends routine screening for type 2 DM every 3 years in all adults starting at 45 years of age[41]. Lab analysis of blood is needed to ensure that the test results are accurate. Glucose measuring devices used are not accurate enough for diagnosis but may be used as a quick indicator of high blood glucose. Testing enables to find and treat diabetes before complications occur and to find and treat prediabetes. This can delay or prevent type 2 diabetes from developing. Mass screening programmes have used glucose measurements of fasting, post prandial or random blood sample[42].

- An A1c test, also called the hemoglobin A1c/HbA1c/ glycohemoglobin test;

- A fasting plasma glucose test;

- An oral glucose tolerance test[43].

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause[44]. Not all tests are recommended for diagnosing all types of diabetes. The random plasma glucose test is sometimes used to diagnose diabetes during a regular health checkup and if it measures above 200 µg per deciliter then the individual also shows the symptoms of DM[43].

Main symptoms of diabetes include increased urination, increased thirst, fatigue, weight loss, blurred vision, increased hunger, and diabetic dermadromes. Any test used to diagnose diabetes requires confirmation with a second measurement unless clear symptoms of diabetes exist[45].

Figure 2 provides the blood test levels for diagnosis of diabetes for a nonpregnant adults and diagnosis of prediabetes[46].

	A1C (%)	Fasting plasma glucose (mg/dL)	Oral glucose tolerance test (mg/dL)
Diabetes	6.5% or above	126% or above	200% or above
Prediabetes	5.7%–6.4%	100%–125%	140%–199%
Normal	About 5%	99% or below	139% or below

Figure 2. Blood test levels for diagnosis of diabetes and prediabetes.

For all three tests, within the prediabetes range, the higher the test result, the greater the risk of diabetes.

5.1. Urine testing

Urine tests are cheap and convenient, but the diagnosis of urine testing cannot be based on urine testing alone since there may be false positives and false negatives. They can be used in population screening surveys. Urine is tested for the presence of glucose and ketones.

5.1.1. Glucosuria

Benedicts qualitative test detects any reducing substance in urine and dipstick method which is more specific and sensitive method.

5.1.2. Ketonuria

Rothera's test and Strip test are performed for the detection of ketone bodies[46].

6. Clinical features of DM

6.1. Type 1 DM

Patients of type 1 DM usually manifest at the early age, generally below 35 years of age. The onset of symptoms is often abrupt. At presentation, patients have polyuria, polydipsia, polyphgia, fatigue, and weight loss. Type 1 diabetics are often first diagnosed when they present with DKA. The symptoms could be dry skin, numbness or lack of sensation in the feet, rapid deep breathing, vomiting and abdominal pain (Figure 3).

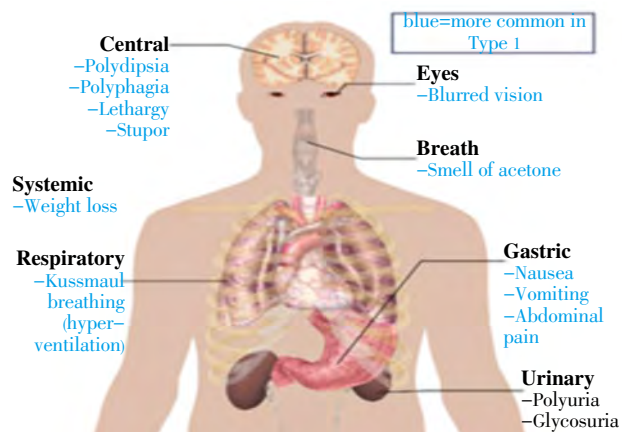


Figure 3. Main symptoms of diabetes mellitus.

6.2. Type 2 DM

This form of diabetes generally manifests in middle life or beyond, usually above the age of 40. The onset of symptoms in type 2 DM is slow and insidious. Generally the patient is asymptomatic when the diagnosis is made on the basis of glycosuria or hyperglycemia during physical examination, or may present with polyuria and polydipsia. Major symptoms include tiredness, lethargy, itching, skin infections, blurred vision, mood swings, headache, dizziness and leg cramps.

Metabolic complications like ketoacidosis are infrequent[5].

7. Complications of DM

7.1. Acute metabolic complications

7.1.1. DKA

It is one of the acute metabolic complication of diabetes. DKA is characterized by uncontrolled hyperglycemia, acidosis and increased level of ketone bodies. Decreased effective insulin concentration and increased concentration of counter regulatory hormone lead to ketosis. Patients with ketosis have autoimmune type 1 diabetes[47]. Infection is the most common precipitating factor in the development of DKA[48].

7.1.2. Hyperglycemia hyperosmolar state (HHS)

Differences in insulin availability and dehydration due to diuresis distinguishes HHS from ketoacidosis[47]. Sustained hyperglycemic diuresis results in severe dehydration. The patient is unable to drink sufficient water to maintain urinary fluid loss. Plasma osmolality and blood sugar level is very high. HHS is usually seen in patient with type 2 DM[49,50]. Insulin levels in HHS prevents lipolysis and ketogenesis[51].

7.1.3. Hypoglycemia

In those treated for diabetes, a diagnosis of hypoglycemia can be made based on the presence of a low blood sugar alone. The episode may develop in patients with type 1 DM. Alteration of consciousness occurs or even it may be lost in extreme cases, leading to permanent brain damage, rebound hyperglycemia and death. The variety of interactions may cause identification difficulty in many instances[52].

7.1.4. Respiratory infections

In diabetes patients, alteration in host defence mechanism leads to hyperglycemia, inflammation and increased susceptibility to infections. There is an impairment in the function of respiratory epithelium and ciliary movement[53,54].

7.1.5. Periodontal disease

Diabetes is also associated with gum diseases and may make diabetes more difficult to treat[55,56].

7.2. Late systemic complications

7.2.1. Atherosclerosis

DM of both type 1 and 2 accelerates the development of atherosclerosis so that consequent lesions appear earlier than in the general population and associated with ulceration, calcification and thrombosis[57].

7.2.2. Diabetic microangiopathy

It is characterized by the basement membrane thickening of small blood vessels and capillaries. Thickening is mainly due to the increased glycosylation of haemoglobin and other proteins like collagen and basement membrane material.

The pathogenic basis behind microangiopathy is the recurrent hyperglycemia[58].

7.2.3. Diabetic nephropathy

Specific renal functional and morphological alterations lead to diabetic nephropathy and are characterized by hyperfiltration of glomerulus, albuminuria, renal hypertrophy etc. Initially there is an elevation of renal plasma flow and glomerular filtration rate. Glomerular hypertension and renal insufficiency accelerates kidney failure[59].

7.2.4. Diabetic retinopathy

It is a leading cause of blindness. Progression is from mild non proliferative abnormalities to severe proliferative diabetic nephropathy[60].

7.2.5. Diabetic neuropathy

It is heterogeneous and may affect all part of the nervous system, but symmetric peripheral neuropathy is most characteristic. It may be local or diffuse[61].

8. Therapy for DM

Diet therapy is important for the prevention as well as the treatment of all stages of type 2 diabetes. Till it continues to remain high controversial and poorly understood. In majority of the individuals with type 2 DM, if obesity seems along with hyperglycemia, weight reduction is the major goal of dietary therapy[62].

Exercise helps to prevent type 2 DM and control all types of diabetes cases. Muscular sensitivity to insulin can be improved by physical activity. The mechanisms involved are increased blood flow to the tissues and reduced free fatty acid and intra abdominal fat level[63].

8.1. Oral hypoglycemic drugs

8.1.1. Sulfonylureas and the newer glitinides

Sulfonylureas have been used to treat type 2 diabetes since 1942 and require functional pancreatic beta cells for their hypoglycemic effect[64,65]. They have an islet beta cytotropic activity[66]. The meglitinides are relatively new class of insulin secretagogues[67]. Both of them act by inducing insulin secretion. The glitinides have a more rapid action of onset and shorter duration of effect than sulfonylureas and are given before a meal to stimulate prandial release of insulin. The average decrease in HgA1c is 1–2 mg/dL. Both these medications can lead to hypoglycemia and weight gain[68].

8.1.2. Biguanides—metformin

They stimulate peripheral utilization of glucose, increase the sensitivity of muscle to insulin action and reduce the intestinal absorption of glucose and leads to an average decrease in HgA1c of 1–2 mg/dL by reducing hepatic gluconeogenesis[69]. Patients of renal or hepatic disease, hypoxic pulmonary disease or heart failure are predisposed to lactic acidosis because of reduced drug elimination or

reduced tissue oxygenation. Alcohol ingestion may also precipitate lactic acidosis^[70]. Metformin is an insulin sparing agent and does not increase weight or provoke hyperglycemia. It should be given first line in obese type 2 diabetics^[71].

8.1.3. α -glucosidase inhibitors (acarbose and miglitol)

α -Glucosidase inhibitors act by inhibiting absorption of carbohydrates. Acarbose also inhibits α -amylase. On average lower HgA1c by 0.5–1.0 mg/dL. Its use is limited by disagreeable gastrointestinal symptoms^[72]. These drugs are contraindicated in patients with inflammatory bowel disease and renal impairment. Acarbose should be used with caution in the presence of hepatic diseases^[67].

8.1.4. Thiazolidinediones (rosiglitazone and pioglitazone)

Thiazolidinediones appears to act by binding to the peroxisome proliferator activator receptor- γ ^[73,74]. They increase the peripheral sensitivity to insulin, reduce hepatic glucose output, and increase peripheral glucose disposal^[68]. The overall effect on HbA1c is a 1% to 1.5% reduction and they increase high density lipoprotein cholesterol by 3–9 mg/dL^[75]. Glitazones are contraindicated in children, lactating mother, in liver and heart failure cases^[76].

8.1.5. Incretin mimetic (exenatide)

Exenatide is a long acting glucagon-like peptide-1 analogue^[77]. It enhances glucose-dependent insulin secretion. Food and Drug Administration approved for use as an adjunct for those failing oral agents. Major adverse effects include nausea, vomiting and hypoglycemia. It has similar efficacy to bedtime insulin (without the weight gain) when added to failing oral regimen, but substantially more expensive^[71].

8.1.6. Amylin analogue (pramlintide)

It suppresses postprandial glucagon secretion and slows gastric emptying. The level HgA1c decreased on average 0.1–0.6 mg/dL. Because of the risk of hypoglycemia insulin doses should be decreased by 50% or more^[78].

8.2. Insulin

Increase in blood glucose level promotes both synthesis and secretion of insulin from beta cells. Insulin has many formulations. Indications for starting insulin include new diagnosis of severe, symptomatic hyperglycemia, co-morbid conditions such as renal or liver disease, congestive heart failure, active infection that may make control difficult with oral medications, pregnancy, diabetic coma, precoma, and intolerance to oral medications. Formulations of insulin varies in their time to peak activity and duration of action. Patient may need only long-acting insulin in the early stages of type 2 DM. As diabetes progresses will likely need meal time and long-acting insulin to adequately control sugars. Typical starting insulin dose is 10–20 units/d. Therapy has to be individualized and no fixed schedule is possible. Insulin use results in weight gain, allergy, resistance and can lead to hypoglycemia^[78,79].

9. Plant remedies in the management of DM

Herbs are used by the mankind since its origin on the earth for alleviating ailments and for the maintenance of general health. Since ancient times, plants remained major natural resource in the world^[80]. Mainly tribes provided the knowledge base regarding medicinal properties of the herbs and these plants have a great demand in both developed and developing countries^[81]. World Health Organization estimated that 80% world's population relies on traditional medicines to meet their primary health care needs, most types of which use remedies from plants. Even the modern pharmacopoeia still contains at least 25% of drugs derived from plants and many others which are semisynthetic, built on prototype compounds isolated from plants^[80]. Recent studies suggest that over 9000 herbs have known medicinal applications among various cultures and countries. Different indigenous medicinal systems such as Allopathy, Siddha, Ayurveda and Unani use several plant species for the treatment of diseases^[82,83]. In recent times, it is imperative that all systems of traditional plant medicines prevailing in the world need to be encouraged if we intend to find cure for those diseases where modern synthetic medicines have failed or where the modern synthetic drugs are beyond the reach of the poor nations^[84]. In India, traditional plant remedies have been used in the treatment of various diseases since the time of Charaka and Shusrutha^[85]. India has a special position in area of herbal medicines, since it is one of the few countries which are capable of cultivating most of the important plants used both in modern and traditional system of medicine^[85]. Demand for herbal medicine sector is growing fast, increasing by 12%–15% value per year^[80].

DM is a disease characterized by impairment of body's normal ability to metabolise or utilize food. During Second World War, when insulin was not available in many countries, research was made for an insulin substitute from plant sources. Many plant species are known in folk medicines of different cultures which have been used for their hypoglycemic effects, a property which reduces the blood sugar concentration. These plants have been found to be useful for the treatment of diabetes^[84]. From ancient times, a number of medicinal plants and their formulations used in the treatment of diabetes in Ayurvedic and ethnomedicinal practices^[82]. Various synthetic drugs developed for the treatment of diabetes, but their use is limited because of their side effects and cost. The popularity of plant medicines due to their lesser side effects and toxicity, led to an increase in the number of herbal drug industries. Indian flora provides great possibilities for the development of new compounds with important medicinal applications. The phytoconstituents showing hypoglycemic effect includes flavanoids, alkaloids, carbohydrates, glycosides, steroids, peptides, lipids *etc*^[86]. Numerous herbs remain potent candidates for antidiabetic drug development. Clinical data begins to emerge, which supports antidiabetic properties of these drugs^[87].

Medicinal plants list with proven antidiabetic and related beneficial effects and of herbal drugs used in the treatment of diabetes are compiled in Table 2.

Table 2

Medicinal plants with antidiabetic potential.

Plant name	Family	Part of the plant used
<i>Acacia arabica</i> [88]	Leguminosae	Bark
<i>Acacia catechu</i> Wild.[89]	Leguminosae	Bark
<i>Aloe vera</i> [90]	Liliaceae	Leaf
<i>Aegle marmelos</i> [91]	Rutaceae	Leaf
<i>Aerva lanata</i> Linn.[92]	Amaranthaceae	Aerial parts
<i>Alpinia calcarata</i> [93]	Zingiberaceae	Rhizome
<i>Azadirachta indica</i> [94]	Meliaceae	Root bark
<i>Allium sativum</i> L.[95]	Liliaceae	bulb
<i>Annona squamosa</i> L[96]	Annonaceae	Leaves
<i>Albizia lebbek</i> [97]	Mimosaceae	Bark
<i>Acacia tortilis</i> [98]	Fabaceae	seed
<i>Aconitum napellus</i> [99]	Leguminosae	Root
<i>Andrographis paniculata</i> [100]	Acanthaceae	Root
<i>Asparagus racemosus</i> [101]	Asparagaceae	Entire plant
<i>Allium cepa</i> [102]	Liliaceae	Bulb
<i>Benincasa hispida</i> [103]	Cucurbitaceous	Stem
<i>Bambusa vulgaris</i> [104]	Poaceae	Leaves
<i>Brassica juncea</i> [105]	Cruciferae	Seed
<i>Boerhaavia diffusa</i> Linn.[106]	Nyctaginaceae	Leaves
<i>Capsicum annum</i> [107]	Solanaceae	Fruit
<i>Catharanthus roseus</i> [108]	Apocynaceae	Flower, leaves, root, stem
<i>Centella asiatica</i> [109]	Umbelliferare	Leaves
<i>Coccinia indica</i> [110]	Cucurbitaceae	Fruit
<i>Coccinia indica</i> [111]	Cucurbitaceae	Leaves
<i>Emblica officinalis</i> [112]	Euphorbiaceae	Fruit
<i>Eugenia jambolana</i> [113]	Myrtaceae	Seed
<i>Ficus religiosa</i> [114]	Moraceae	Fruit and leaves
<i>Grewia asiatica</i> [115]	Tilliaceae	Fruit, stem bark, leaves
<i>Gymnema sylvestre</i> [116]	Ascleridaceae	Leaves
<i>Hyptis suaveolens</i> [117]	Lamiaceae	Leaves
<i>Jatropha curcas</i> [118]	Euphorbiaceae	Leaves
<i>Mimosa pudica</i> [119]	Fabaceae	Leaves
<i>Moringa oleifera</i> [120]	Moringaceae	Leaves
<i>Terminalia catappa</i> [121]	Combretaceae	Leaves
<i>Tinospora cordifolia</i> [122]	Menispermaceae	Root
<i>Tragia involucrate</i> [123]	Euphorbiaceae	Entire plant

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

Authors are thankful to the Indian Council of Medical Research, New Delhi for providing Senior Research Fellowship (Grant No. 45/31/2010/BMS/TRM) and St. Joseph College of Pharmacy, Cherthala, Alappuzha, Kerala for their kind and support in preparing this review article.

Comments

Background

Diabetes is one of the major health and development challenges of the 21st century. According to the International Diabetes Federation, there are currently 371 million people living with diabetes and another 28 million people are at

high risk of developing the disease. Apart from conventional allopathic medicines, traditional/alternative therapy plays a significant role in treating DM.

Research frontiers

The authors have put the effort and compiled all the information about DM and plants showed antidiabetic effect which shall be a report of plants used in the treatment of DM.

Related reports

It is not a research work but the authors have summarized the information about DM and medicinal plants.

Innovations & breakthroughs

Authors have attempted to compile the types, pathophysiology, complications and treatment of DM. All this information will help researchers to explore its scientific evidence based on modern era.

Applications

It will be significant to know traditional uses and phytoconstituents present in different plants to expand unexplored area by scientific evaluation.

Peer review

This is a good review paper in which the authors have reviewed about DM and the role of medicinal plants for the treatment. I recommend this article to be published.

References

- [1] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; **26**: 3160–3167.
- [2] American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2009; **32**(Suppl 1): S62–S67.
- [3] Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. *Rang and Dale's pharmacology*. 7th ed. London: Churchill Livingstone; 2012, p. 377.
- [4] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 842.
- [5] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 848.
- [6] Tripathi KD. *Essentials of medical pharmacology*. 6th ed. New Delhi: Jaypee Brothers Medical Publishers; 2008, p. 263–265.
- [7] Boon NA, Colledge NR, Walker BR, Hunter J. *Davidson's principles and practice of medicine*. 20th ed. London: Churchill Livingstone; 2006, p. 821–835.
- [8] Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. *Rang and Dale's pharmacology*. 7th ed. London: Churchill Livingstone; 2012, p. 378.
- [9] Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. *Williams textbook of endocrinology*. 12th ed. Amsterdam: Elsevier; 2012, p. 1371–1435.
- [10] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047–1053.
- [11] Adeghate E, Schattner P, Dunn E. An update on the etiology and

- epidemiology of diabetes mellitus. *Ann N Y Acad Sci* 2006; **1084**: 1–29.
- [12] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2002; **25**(Suppl 1): S5–S20.
- [13] Mealey BL. Diabetes mellitus and oral diseases. American Medical Network. [Online] Available from: <http://www.health.am/db/diabetes-mellitus-and-oral-health/> [Accessed on 15th April, 2014]
- [14] Wells BG, Dipiro JT, Schwinghammer TL, Dipiro CV. *Pharmacotherapy principles and practice*. 7th ed. New York: The McGraw Hill Companies; 2008, p. 645.
- [15] Kumar V, Fausto N, Abbas A. *Robbins & Cotran pathological basics of disease*. 7th ed. Philadelphia: Saunders; 2004, p. 1190–1191.
- [16] Pittas AG, Greenberg AS. *Contemporary diagnosis and management of diabetes*. Newtown: Handbooks in Health Care Co.; 2003.
- [17] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26**(1): S5–S20.
- [18] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 844.
- [19] Mathis D, Vence L, Benocit C. Beta cell death during progression to diabetes. *Nature* 2001; **414**: 792–798.
- [20] Kumar V, Fausto N, Abbas A. *Robbins & Cotran pathological basics of disease*. 7th ed. Philadelphia: Saunders; 2004, p. 1193–1194.
- [21] Pietropaolo M, Eisenbarth GS. Autoantibodies in human diabetes. *Curr Dir Autoimmun* 2001; **4**: 252–282.
- [22] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 845.
- [23] Greene RJ, Harris ND. *Pathology and therapeutics for pharmacists: a basis for clinical pharmacy practice*. 3rd ed. London: Pharmaceutical Press; 2008.
- [24] Todd JA, Wicker LS. Genetic protection from the inflammatory disease type 1 diabetes in humans and animal models. *Immunity* 2001; **15**(3): 387–395.
- [25] Kumar V, Fausto N, Abbas A. *Robbins & Cotran pathological basics of disease*. 7th ed. Philadelphia: Saunders; 2004, p. 1194.
- [26] Jaeckel E, Manns M, Von Herrath M. Viruses and diabetes. *Ann N Y Acad Sci* 2002; **958**: 7–25.
- [27] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 846.
- [28] Wells BG, Dipiro JT, Schwinghammer TL, Dipiro CV. *Pharmacotherapy principles and practice*. 7th ed. New York: The McGraw Hill Companies; 2008, p. 646.
- [29] Kumar V, Fausto N, Abbas A. *Robbins & Cotran pathological basics of disease*. 7th ed. Philadelphia: Saunders; 2004, p. 1195.
- [30] Elbein SC. Perspective: the search for genes for type 2 diabetes in the post genome era. *Endocrinology* 2002; **143**: 2012–2018.
- [31] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 847.
- [32] Saltiel AR. Series introduction: the molecular and physiological basis of insulin resistance: emerging implications for metabolic and cardiovascular diseases. *J Clin Invest* 2000; **106**: 163–164.
- [33] Kumar V, Fausto N, Abbas A. *Robbins & Cotran pathological basics of disease*. 7th ed. Philadelphia: Saunders; 2004, p. 1196.
- [34] Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000; **106**: 473–481.
- [35] Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000; **106**: 171–176.
- [36] Saltiel AR. You are what you secrete. *Nat Med* 2001; **7**: 887–888.
- [37] Steyn NP, Mann J, Bennet PH, Temple N, Zimmet P, Tumilehto J, et al. Diet, nutrition and prevention of type 2 diabetes. *Public Health Nutr* 2004; **7**: 147–165.
- [38] Caro JF, Dohm LG, Pories WJ, Sinha MK. Cellular alterations in liver, skeletal muscle, and adipose tissue responsible for insulin resistance in obesity and type 2 diabetes. *Diabetes Metab Rev* 1989; **5**: 665–689.
- [39] Krotkiewski M, Lönnroth P, Mandroukas K, Wroblewski Z, Rebuffé-Scrive M, Holm G, et al. The effects of physical training on insulin secretion and effectiveness and on glucose metabolism in obesity and type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1985; **28**: 881–890.
- [40] Mourier A, Gautier JF, De Kerviler E, Bigard AX, Villette JM, Garnier JP, et al. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements. *Diabetes Care* 1997; **20**: 385–391.
- [41] Wells BG, Dipiro JT, Schwinghammer TL, Dipiro CV. *Pharmacotherapy principles and practice*. 7th ed. New York: The McGraw Hill Companies; 2008, p. 647.
- [42] Park K. *Park's textbook of preventive and social medicine*. 20th ed. Jabalpur: M/s Banarsidas Bhanot Publishers; 2009, p. 341–345.
- [43] National Diabetes Information Clearinghouse. Diagnosis of diabetes and prediabetes. Bethesda: National Diabetes Information Clearing House. [Online] Available from: <http://diabetes.niddk.nih.gov/dm/pubs/diagnosis/> [Accessed on 16th April, 2014]
- [44] Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010; **362**: 800–811.
- [45] Cooke DW, Plotnick L. Type 1 diabetes mellitus in pediatrics. *Pediatr Rev* 2008; **29**: 374–384.
- [46] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 851–852.
- [47] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32**: 1335–1343.
- [48] Ennis ED, Stahl EJ, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. *Diabetes Rev* 1994; **2**: 115–126.
- [49] Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. *Endocrinol Metab Clin North Am* 2000; **29**: 683–705.
- [50] Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In: Kahn CR, Weir GC, editors. *Joslin's diabetes mellitus*. 13th ed. Philadelphia: Lea & Febiger; 1994, p. 738–770.
- [51] Scott A. The management of the hyperosmolar hyperglycaemic

- state (HHS) in adults with diabetes. London: Diabetes UK; 2012. [Online] Available from: https://www.diabetes.org.uk/About_us/What-we-say/Improving-diabetes-healthcare/Management-of-the-hyperosmolar-hyperglycaemic-state-HHS-in-adults-with-diabetes/ [Accessed on 16th April, 2014]
- [52] Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009; **94**: 709–728.
- [53] Ahmed MS, Reid E, Khardori N. Respiratory infections in diabetes: reviewing the risks and challenges. *J Respir Dis* 2008; **29**: 285–293.
- [54] Ljubic S, Balachandran A, Pavlic-Renar I, Barada A, Metelko Z. Pulmonary infections in diabetes mellitus. *Diabetologia Croatica* 2004; **33**(4): 115–124.
- [55] Mealey BL. Periodontal disease and diabetes. A two-way street. *J Am Dent Assoc* 2006; **137**(Suppl 1): 26S–31S.
- [56] Lakschevitz F, Aboodi G, Tenenbaum H, Glogauer M. Diabetes and periodontal diseases: interplay and links. *Curr Diabetes Rev* 2011; **7**: 433–439.
- [57] Mohan H. *Textbook of pathology*. 5th ed. New Delhi: Jaypee Brothers Medical Publishers; 2005, p. 850.
- [58] Gärtner V, Eigtler TK. Pathogenesis of diabetic macro and micro angiopathy. *Clin Nephrol* 2008; **70**: 1–9.
- [59] Parchwani DN, Upadhyah AA. Diabetic nephropathy: progression and pathophysiology. *Int J Med Sci Public Health* 2012; **1**(2): 59–70.
- [60] Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Diabetic retinopathy. *Diabetes Care* 2003; **26**(Suppl 1): S99–S102.
- [61] Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by American diabetes association. *Diabetes Care* 2005; **28**: 956–962.
- [62] Grundy SM. Diet therapy in diabetes mellitus: is there a single best diet? *Diabetes Care* 1991; **14**: 796–801.
- [63] Colberg SR, Grieco CR. Exercise in the treatment and prevention of diabetes. *Curr Sports Med Rep* 2009; **8**(4): 169–175.
- [64] Lebovitz HE. *Insulin secretagogues: sulfonylureas, meglitinides, and phenylalanine derivatives*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004, p. 1108–1118.
- [65] Groop LC, Ratheiser K, Luzi L, Melander A, Simonson DC, Petrides A, et al. Effect of sulphonylureas on glucose-stimulated insulin secretion in healthy and non-insulin-dependent diabetes subjects: a dose response study. *Acta Diabetol* 1991; **28**: 162–168.
- [66] Barar FS. *Essentials of pharmacotherapeutics*. 3rd ed. New Delhi: S. Chand and Company Ltd; 2005, p. 346.
- [67] Katzung BG. *Basic and clinical pharmacology*. 10th ed. New York: The McGraw Hill Companies; 2007, p. 696.
- [68] Smith DG, Aronson JK. *Oxford textbook of clinical pharmacology and drug therapy*. 3rd ed. Oxford: Oxford University Press; 2002, p. 324.
- [69] Barar FS. *Essentials of pharmacotherapeutics*. 3rd ed. New Delhi: S. Chand and Company Ltd; 2005, p. 347.
- [70] Sharma HL, Sharma KK. *Principles of pharmacology*. 2nd ed. Hyderabad: Paras Medical Publisher; 2011, p. 638.
- [71] Katzung BG. *Basic and clinical pharmacology*. 10th ed. New York: The McGraw Hill Companies; 2007, p. 698–702.
- [72] van de Laar FA. Alpha glucosidase inhibitor in the early treatment of type 2 diabetes. *Vasc Health Risk Manag* 2008; **4**: 1189–1195.
- [73] Spiegelman BM. PPAR- γ : adipogenic regulator and thiazolidinedione receptor. *Diabetes* 1998; **47**: 507–514.
- [74] Lehman JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome-proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995; **270**: 12953–12956.
- [75] Wells BG, Dipiro JT, Schwinghammer TL, Dipiro CV. *Pharmacotherapy principles and practice*. 7th ed. New York: The McGraw Hill Companies; 2008, p. 657.
- [76] Sharma HL, Sharma KK. *Principles of pharmacology*. 2nd ed. Hyderabad: Paras Medical Publisher; 2011, p. 639–640.
- [77] Boon NA, Colledge NR, Walker BR, Hunter J. *Davidson's principles and practice of medicine*. 20th ed. London: Churchill Livingstone; 2006, p. 834.
- [78] Madison Clinic. Guidelines on diabetes: diagnosis and management. Seattle: Madison Clinic; 2009. [Online] Available from: <http://depts.washington.edu/madclin/providers/guidelines/diabetes.html> [Accessed on 16th April, 2014]
- [79] Barar FS. *Essentials of pharmacotherapeutics*. 3rd ed. New Delhi: S. Chand and Company Ltd; 2005, p. 340–342.
- [80] Kalia AN. *A textbook of industrial pharmacognosy*. 1st ed. New Delhi: CBS Publishers & Distributors; 2005, p. 1–9.
- [81] Yirga G, Teferi M, Kasaye M. Survey of medicinal plants used to treat human ailments in Hawzen district, Northern Ethiopia. *Int J Biodivers Conserv* 2011; **3**(13): 709–714.
- [82] Lakshmi SM, Rani SK, Reddy UK. A review on diabetes mellitus and the herbal plants used for its treatment. *Asian J Pharm Clin Res* 2012; **5**: 15–21.
- [83] Chatterje I, Chakravarty AK, Gomesa A. *Daboia russellii* and *Naja kaouthia* venom neutralization by lupeol acetate isolated from the root extract of Indian sarsaparilla *Hemidesmus indicus* R.Br. *J Ethnopharmacol* 2006; **106**: 38–43.
- [84] Handa SS, Kapoor VK. *Textbook of pharmacognosy*. 2nd ed. Delhi: Vallabh Prakashan; 2003, p. 3–8.
- [85] Prabhakar PK, Doble M. Mechanism of action of natural products used in the treatment of diabetes mellitus. *Chin J Integr Med* 2011; **17**(8): 563–574.
- [86] Dewanjee S, Das AK, Sahu R, Gangopadhyay M. Antidiabetic activity of *Diospyros peregrina* fruit: effect on hyperglycemia, hyperlipidemia and augmented oxidative stress in experimental type 2 diabetes. *Food Chem Toxicol* 2009; **47**: 2679–2685.
- [87] Vuksan V, Sievenpiper JL. Herbal remedies in the management of diabetes: lessons learned from the study of ginseng. *Nutr Metab Cardiovasc Dis* 2005; **15**: 149–160.
- [88] Yasir M, Prateek Jain D, Kharya MD. Hypoglycemic and antihyperglycemic effect of different extracts of acacia arabica lamk bark in normal and alloxan induced diabetic rats. *Inter J Phytomed* 2010; **2**: 133–138.
- [89] Jarald E, Joshi SB, Jain DC. Biochemical study on the hypoglycaemic effects of extract and fraction of *Acacia catechu* willd in alloxan-induced diabetic rats. *Int J Diabetes Metabolism* 2009; **17**: 63–69.
- [90] Rajasekaran R, Satishsekar D. Therapeutic evaluation of aloe vera leaf gel extract on glycoprotein components in rats with streptozotocin diabetes. *J Pharmacol Toxicol* 2007; **2**: 380–385.

- [91] Arumugam S, Kavimani S, Kadalmanic B, Ahmed AB, Akbarsha MA, Rao MV. Antidiabetic activity of leaf and callus extracts of *Aegle marmelos* in rabbit. *ScienceAsia* 2008; **34**: 317–321.
- [92] Appia Krishnan G, Rai VK, Nandy BC, Meena KC, Dey S, Tyagi PK, et al. Hypoglycemic and antihyperlipidaemic effect of ethanolic extract of aerial parts of *Aerva lanata* Linn. in normal and alloxan induced diabetic rats. *Int J Pharm Sci Drug Res* 2009; **1**: 191–194.
- [93] Raj N, Nadeem S, Jain S, Raj C, Prithwish Nandi KC. Ameliorative effects of *Alpinia calcarata* in alloxan-induced diabetic rats. *Dig J Nanomater Bios* 2011; **6**: 991–997.
- [94] Patil P, Patil S, Mane A, Verma S. Antidiabetic activity of alcoholic extract of neem (*Azadirachta indica*) root bark. *Natl J Physiol Pharm Pharmacol* 2013; **3**: 142–146.
- [95] Eidi A, Eidi M, Esmaeili E. Antidiabetic effect of garlic (*Allium sativum* L.) in normal and streptozotocin-induced diabetic rats. *Phytomedicine* 2006; **13**: 624–629.
- [96] Tomar RS, Sisodia S. Antidiabetic activity of *Annona squamosa* L. in experimental induced diabetic rats. *Int J Pharm Biol Arch* 2012; **3**: 1492–1495.
- [97] Syiem D, Khup PZ, Syiem AB. Evaluation of anti-diabetic potential of *Albizia lebbek* bark in normal and alloxan-induced diabetic mice. *Pharmacologyonline* 2008; **3**: 563–573.
- [98] Agrawal NK, Gupta U. Evaluation of hypoglycemic and antihyperglycemic effects of *Acacia tortilis* seed extract in normal and diabetic rats. *Inter J PharmTech Res* 2013; **5**: 330–336.
- [99] Chhetree RR, Dash GK, Mondal S, Acharyya S. Studies on the hypoglycaemic activity of *Aconitum napellus* L. roots. *Drug Invention Today* 2010; **2**: 343–346.
- [100] Rao NK. Anti-hyperglycemic and renal protective activities of *Andrographis paniculata* roots chloroform extract. *Iran J Pharmacol Therap* 2006; **5**: 47–50.
- [101] Vadivelan R, Dipanjan M, Umasankar P, Dhanabal SP, Satishkumar MN, Antony S, et al. Hypoglycemic, antioxidant and hypolipidemic activity of *Asparagus racemosus* on streptozotocin-induced diabetic in rats. *Adv Appl Sci Res* 2011; **2**: 179–185.
- [102] El-Demerdash FM, Yousef MI, Abou El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. *Food Chem Toxicol* 2005; **43**: 57–63.
- [103] Mohana Rupa L, Mohan K. Hypoglycaemic effect of aqueous extract of *Benincasa hispida* in rabbits. *Inter Ayur Med J* 2013; **1**: 1–5.
- [104] Senthilkumar MK, Sivakumar P, Changanakkattil F, Rajesh V, Perumal P. Evaluation of anti-diabetic activity of *Bambusa vulgaris* leaves in streptozotocin induced diabetic rats. *Inter J Pharm Sci Drug Res* 2011; **3**: 208–210.
- [105] Thirumalai T, Therasa SV, Elumalai E, David E. Hypoglycemic effect of *Brassica juncea* (seeds) on streptozotocin induced diabetic male albino rat. *Asian Pac J Trop Biomed* 2011; **1**: 323–325.
- [106] Nalamolu RK, Boini KM, Nammi S. Effect of chronic administration of *Boerhaavia diffusa* Linn. leaf extract on experimental diabetes in rats. *Trop J Pharm Res* 2004; **3**: 305–309.
- [107] Kwon Y, Apostolidis E, Shetty K. Evaluation of pepper (*Capsicum annum*) for management of diabetes and hypertension. *J Food Biochem* 2007; **31**: 370–385.
- [108] Vega-Avila E, Cano-Velasco JL, Alarcon-Aguilar FJ, Fajardo Ortiz MC, Almanza-Perez JC, Roman-Ramos R. Hypoglycemic activity of aqueous extracts from *Catharanthus roseus*. *Evid Based Complement Alter Med* 2012; doi: 10.1155/2012/934258.
- [109] Chauhan PK, Pandey IP, Dhatwalia VK. Evaluation of the anti-diabetic effect of ethanolic and methanolic extracts of *Centella asiatica* leaves extract on alloxan induced diabetic rats. *Adv Biol Res* 2010; **4**: 27–30.
- [110] Gunjan M, Jana GK, Jha AK, Mishra U. Pharmacognostic and antihyperglycemic study of *Coccinia indica*. *Inter J Phytomed* 2010; **2**: 36–40.
- [111] Ghosh S, Roy T. Evaluation of antidiabetic potential of methanolic extract of *Coccinia indica* leaves in streptozotocin induced diabetic rats. *Int J Pharm Sci Res* 2013; **4**: 4325–4328.
- [112] Tigar PR, Shah KV, Patel VP, Desai TR, Goyal RK. Investigation into mechanism of action of anti-diabetic activity of *Embilca officinalis* on streptozotocin induced type I diabetic rat. *Res J Pharm Biol Chem Sci* 2010; **1**(4): 672–682.
- [113] Sridhar SB, Sheetal UD, Pai MR, Shastri MS. Preclinical evaluation of the antidiabetic effect of *Eugenia jambolana* seed powder in streptozotocin-diabetic rats. *Braz J Med Biol Res* 2005; **38**: 463–468.
- [114] Choudhary S, Pathak AK, Khare S, Kushwah S. Evaluation of antidiabetic activity of leaves and fruits of *Ficus religiosa* Linn. *Int J Pharm Life Sci* 2011; **2**: 1325–1327.
- [115] Parveen A, Irfan M, Mohammad F. Antihyperglycemic activity in *Grewia asiatica*, a comparative investigation. *Int J Pharm Pharm Sci* 2012; **4**: 210–213.
- [116] Verma N, Shakya VK, Saxena RC. Antidiabetic activity of glycoside isolated from *Gymnema sylvestre* in streptozotocin induced diabetic rats. *Asian J Chem* 2008; **20**(7): 5033–5036.
- [117] Danmalam UH, Abdullahi LM, Agunu A, Musa KY. Acute toxicity studies and hypoglycemic activity of the methanol extract of the leaves of *Hyptis suaveolens* Poit. (Lamiaceae). *Niger J Pharm Sci* 2009; **8**: 87–92.
- [118] Mishra SB, Vijayakumar M, Ojha SK, Verma A. Antidiabetic effect of *Jatropha curcas* L. leaves extract in normal and alloxan-induced diabetic rats. *Int J Pharm Sci* 2010; **2**: 482–487.
- [119] Sutar NG, Sutar UN, Behera BC. Antidiabetic activity of the leaves of *Mimosa pudica* Linn. in albino rats. *J Herbal Med Toxicol* 2009; **3**: 123–126.
- [120] Jaiswal D, Kumar Rai P, Kumar A, Mehta S, Watal G. Effect of *Moringa oleifera* Lam. leaves aqueous extract therapy on hyperglycemic rats. *J Ethnopharmacol* 2009; **123**: 392–396.
- [121] Ahmed SM, Vrushabendra Swamy BM, Gopkumar P, Dhanapal R, Chandrashekara VM. Anti-diabetic activity of *Terminalia catappa* Linn. leaf extracts in alloxan-induced diabetic rats. *Iran J Pharmacol Therap* 2005; **4**: 36–39.
- [122] Stanely P, Prince M, Menon VP. Hypoglycaemic and other related actions of *Tinospora cordifolia* roots in alloxan-induced diabetic rats. *J Ethnopharmacol* 2000; **70**: 9–15.
- [123] Farook SM, Atlee CW. Antidiabetic and hypolipidemic potential of *Tragia involucrata* Linn. in streptozotocin-nicotinamide induced type II diabetic rats. *Int J Pharm Pharm Sci* 2011; **3**: 103–109.