Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

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

Document heading

Diabetes mellitus: An overview on its pharmacological aspects and reported medicinal plants having antidiabetic activity

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ARTICLE INFO

ABSTRACT

Diabetes mellitus is not a single disease but is a group of metabolic disorders affecting a huge number of population in the world. It is mainly characterized by chronic hyperglycemia, resulting from defects in insulin secretion or insulin action. It is predicated that the number of diabetes person in the world could reach upto 366 million by the year 2030. Even though the cases of diabetes are increasing day by day, except insulin and oral hypoglycemic drugs no other way of treatment has been successfully developed so far. Thus, the objective of the present review is to provide an insight over the pathophysiological and etiological aspects of diabetes mellitus along with the remedies available for this metabolic disorder. The review also contains brief idea about diabetes mellitus and the experimental screening model with their relevant mechanism and significance mainly used nowadays. Alloxan and streptozotocin are mainly used for evaluating the antidiabetic activity of a particular drug. This review contain list of medicinal plants which have been tested for their antidiabetic activity in the alloxan induced diabetic rat model. From the available data in the literature, it was found that plant having antidiabetic activity is mainly due to the presence of the secondary metabolite. Thus, the information provided in this review will help the researchers for the development of an alternative methods rather than insulin and oral hypoglycemic agents for the treatment of diabetes mellitus, which will minimize the complication associated with the diabetes and related disorder.

1. Introduction

Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of population in the world[1]. Diabetes mellitus is not a single disorder but it is a group of metabolic disorder characterised by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat, and protein metabolism. When ketones body is present in the blood or urine, it is called ketoacidosis, hence proper treatment should be taken immediately, else it can leads to other diabetic complications[2]. Diabetes mellitus has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications[3]. Diabetes is mainly attributed to the rapid rise in unhealthy life style, urbanization and aging. Hyperglycaemia which is the main symptom of diabetes mellitus generates reactive oxygen species (ROS) which cause lipid peroxidation and membrane damage. ROS plays an important role in the development of secondary complications in diabetes mellitus such as cataract, neuropathy and nephropathy. Antioxidants protect β−cells from oxidation by inhibiting the peroxidation chain reaction and thus they play an important role in the diabetes. Plants containing natural antioxidants such as tannins, flavonoids, vitamin C and E can preserve β−cell function and prevent diabetes induced ROS formation. Polyphenols, which are classified into many groups such as flavonoids, tannins and stilbenes, have been known as health−beneficial properties, which include free radical scavenging, inhibition of hydrolytic and oxidative enzymes, anti−inflammatory action and antidiabetogenic potentiality[4,5]. Aldose reductase as a key enzyme, catalyze the reduction of glucose to sorbitol and is associated in the chronic complications of diabetes

such as peripheral neuropathy and retinopathy. Use of aldose reductase inhibitors and α –glucosidase inhibitors has been reported for the treatment of diabetic complications[6].

The aim of this review is to provide the available data about diabetes mellitus, its epidemiology, causes of diabetes, pathophysiology, available treatment, diagnostic criteria, major available screening model system, herbal approach to treat diabetes and pharmacologically tested plant material. The review also covers certain plant materials which were screened in alloxan induced diabetic rat's models and the data information were collected from the available litreature search published in last three year using alloxan induced diabetic rat model. Moreover, only subacute and chronic diabetic study of the plant material were included in the present review.

2. 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" (refers to the presence of sugar in the urine). Greeks had knowledge of a disease accompanied by polyurea and wasting of body, whereas Aretaeus of Cappadocia mentioned a disease characterized by thirst and polyurea. Subsequently, the knowledge spreaded to Chinese, Iranians and Arabians. From the Middle East, the knowledge of diabetes mellitus had spread to Spain as a disease characterized by polyurea, polydipsia with sugary flavoured urine. With the discovery of sugar in urine and its detection by laboratory test, the knowledge permeated into the 18th century. The estimated burden of diabetes in India was 22 millions in 1990, 28 million in 1995 and 33 millions in 2000. It is the most common metabolic associated disease in the world. NIDDM is the most common form of diabetes constituting nearly 90% of the diabetic population in any country with varying numbers in different geographical regions[7].

According to ancient Hindu physicians, 'Madhumeha' is a disease in which a patient passes sweet urine and exhibits sweetness all over the body. They had recorded in their observations that 'if too many ants swarm around a spot of urine, then the person have symptoms of diabetes mellitus'[7]. According to World Health Organization projection, the diabetes population is likely to increase to 300 million or more by the year 2025[8]. The current studies in India indicate that there is an alarming rise in prevalence of diabetes which has gone beyond epidemic form to a pandemic one[1]. Globally, diabetes mellitus presents enormous and increasingly important public health issues. The occurrence and consequences associated with diabetes are found to be high in countries like India (31.7%), China (20.8%) and United State of America (17.7%)[9]. It is predicted that by 2030, India, China and the United States will have the largest number of people with diabetes[10]. In most western countries, type 1 diabetes accounts for over 90% of

childhood and adolescent diabetes although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common in youth onset diabetes in certain at risk populations. In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan, which represents approximately one third of cases of type 1 diabetes. Type 1 diabetes is more common in the offspring of diabetic men compared with diabetic women[2].

3. Type of diabetes mellitus

Based upon the etiology, diabetes mellitus can be divided into two main types, Type 1, "Juvenile Diabetes Mellitus" (Insulin Dependent Diabetes Mellitus) and Type 2, "Adult type" (Non–Insulin Dependent Diabetes Mellitus). Type 1 occurs in childhood, mainly due to destruction of pancreatic β –cell islets through autoimmune–mediated, resulting in absolute insulin deficiency. Type 2 is more associated with an adulthood and elderly people, which are mainly due to insulin resistance or abnormal insulin secretion[3,7]. The exact causes of pancreatic failure and insulin resistance are unknown, but they are associated with disease state, environmental impact and food habit. Diabetic patients are more susceptible to various type of infection such as skin diseases and carbuncles[7]. Other type of diabetes is gestational diabetes which is mainly associated with pregnancy. Genetic defects of β –cell function or insulin action is also a type of diabetes mellitus commonly called maturity onset diabetes[2]. Neonatal diabetes mellitus is also a type of disorder in which Insulin is required for the maintainance of blood glucose level in the first three months of life. It may be associated with intrauterine growth retardation and defects of chromosome[2]. Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterised by progressive non–autoimmune beta–cell failure[2]. Cystic fibrosis related diabetes 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 occurs by other factors like stress or in other case by the uses of medication such as dexamethasone, L–asparaginase, glucocorticoids, cyclosporin or tacrolimus, olanzapine, risperidol, quetiapine and ziprasidone[2].

4. Pathophysiology of diabetes mellitus

Diabetes mellitus has a profound adverse effect on quality of life in terms of social, psychological well–being as well as physical health. Diabetic complications are mainly mediated through oxidative stress such as increased production of ROS or impaired antioxidant defense systems. Enhancement of lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism are the main factors

involved in the development of diabetes[11]. Production of free radicals is also involved in the pathogenesis of various type of disease including diabetes mellitus[12]. Increased formation and accumulation of advanced glycation products (AGEs) is also involved in the diabetic complications, such as retinopathy, neuropathy, and renal dysfunction through a series of pathological changes[13]. Though several hormones are involved in the regulation of blood glucose level, the most important ones are insulin and glucagon. When imbalanced occurs in the level of hormones in the body, sugar starts accumulating in the blood and when concentration of glucone increased in the blood then finally it will passes in urine along with other minerals[7]. In most cases of diabetes, primarily T–cell mediates pancreatic islet β–cell destruction, and becomes clinically symptomatic when 90% of pancreatic beta cells are destroyed. Serological markers such as islet cell, glutamic acid decarboxylase (GAD), IA–2, IA– 2 β, or insulin autoantibodies, are present in 85–90% of individuals when fasting hyperglycemia is detected. Sometimes environmental triggers, such as chemical or viral initiated pancreatic β–cell destruction, which can triger consequences and thereby leads to the cause in diabetes mellitus. From the study it was found that enterovirus infection is also associated with the development of diabetes mellitus[2].

5. Causes of diabetes mellitus

The cause of diabetes depends 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 lifestyle factors and genetics[2]. There are various types of other factors that involved in the development of diabetes which are the genetic material such as chromosomal and mitochondrial DNA mutation. Leprechaunism, Rabson–Mendenhall 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 in the pancrease such as pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, fibrocalculous 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 pancrease such as aromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism and aldosteronoma can also mediate diabete mellitus. There are some other genetic syndromes such as Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, 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[2].

6. Diagnostic feature of diabetes mellitus

Main diagnostic criteria of diabetes are elevated blood glucose level and the presence or absence of symptoms such as polyurea, polydepsia and fatigueness, blurring of vision, and weight loss, in association with glycosuria and ketonuria. 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 $\geqslant$ 200 mg/dL or fasting plasma glucose $\geqslant$ 126 mg/dL and 2–hour postload glucose $\geqslant$ 200 mg/dL during an OGTT were considered as diabetes[2,7]. Sometimes measurement of specific autoantibody markers such as islet cell antibody (ICA), GAD, IA2, IAA and HbA1c 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[2].

7. Experimental models for diabetic mellitus screening

To understand the pathogenesis, complications, and testing of various therapeutic agents appropriate experimental models are needed. Diabetes animal models can be obtained through spontaneously, chemical induced or dietary or surgical manipulations. In recent trends large numbers of new genetically modified animal models including transgenic, generalized knock–out and tissuespecific knockout mice have been used for the screening of antidiabetic drugs[10]. Since the initial findings in 1943 of alloxan induced β–cell necrosis in rabbits, it has been used for inducing experimental diabetes till so far. Alloxan is a uric acid derivative act by selectively destroying the pancreatic beta islets leading to insulin deficiency, hyperglycaemia and ketosis. Because of its low stability, relatively very shorter half–life and acidic nature of solution, intravenous route of administration of alloxan is preferred[14]. Like alloxan, streptozotocin causes hyperglycaemia mainly by its direct cytotoxic action on the pancreatic beta cells. In streptozotocin, nitrosourea moiety is responsible for beta cell toxicity, while deoxyglucose moiety facilitates transport across the cell membrane. Like alloxan, the involvement of free radicals generation and resulting alteration of endogenous scavengers of these reactive species have been reported in streptozotocin induced diabetes. There are various types of Type 2 antidiabetic screening animal model used for the screening of drug such as spontaneous or genetically derived diabetic animals, Diet/nutrition induced diabetic animals, chemically induced diabetic animals,

surgical diabetic animals, transgenic/knock–out diabetic animal models[14].

8. Available therapy for diabetes mellitus

The treatment of diabetes mellitus is considered as the main global problem and successful treatment has yet to be discovered. Eventhough insulin therapy and oral hypoglycemic agents are the first line of treatment for the diabetes mellitus they have some side effects and fail to significantly alter the course of diabetic complications[15].

8.1. Human insulin

Human insulin is a polypeptide, having a molecular weight of about 6 000 Da, consisted of two amino acid chains A and B, which are linked by two disulphide (–S–S–) linkages. Normal human pancreas contains about 8–10 mg of insulin. Insulin is not suitable for oral administration due to inactivation by digestive enzymes. 80% of exerted 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].

8.2. Oral hypoglycemic drugs

Currently available oral therapies for treatment of diabetes mellitus are sulfonylureas, biguanides, α –glucosidase inhibitors, and glinides, which can be used alone or combined with other drugs to achieve better effect. Many of these oral antidiabetic agents have a number of serious adverse effects, thus, the management of diabetes without any side effects is still a challenge[1,8]. Sulphonylureas are useful in the treatment of diabetes which cannot be controlled by diet or other available therapy. Sulphonylureas are absorbed rapidly from the intestine, some important drugs of this group are tolbutamide, chlorpropamide, glibenclamide, tolazamide etc. Biguanides is the other class of oral anti–diabetic agents which control all types of diabetes mellitus. It reduces glucose absorption from the intestine and can also be used to treat mild diabetes during pregnancy[7]. Natural anti–diabetic drugs from medicinal plants, is the other available therapy for the treatment of diabetse mellitus due to their well–known biological activity. Substances extracted from fruiting bodies, cultured mycelia, and culture media have exhibited promising *in vitro* and *in vivo* biological activity including anti–diabetes[13]. There are many herbal formulation available in the market which are used to treat diabetic mellitus such as Diabecon, Diasulin, Pancreatic tonic 180 cp, Chakrapani, Bitter gourd Powder, Dia–care, Diabetes–Daily Care, Gurmar powder, Epinsulin, Diabecure, Diabeta and Syndrex[16]. If the diet of the diabetic patients is not properly controlled, insulin or oral hypoglycemic drugs will not act properly. A diabetic person should take more care about his body weight and food habit, regular exercise can also improve the utilization of the blood glucose through different tissue in the body which can reduces the symptoms of diabetes[7].

9. Herbal remedies for diabetes mellitus

Herbal medications have been used for the treatment of variety of ailments, a huge number of population in the world is entirely dependent on traditional medicines[8,17]. A number of medicinal plants and their formulations are used for treating diabetes in Ayurvedic medicine system as well as in ethnomedicinal practices[1]. In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Shusrutha. From the ethnobotanical information, about 800 plants which may possess anti–diabetic potential have been found[7,15,18]. Several plants have been used as dietary adjuvant and in treating the number of diseases even without any knowledge on their proper functions and constituents. This practice may be due to its fewer side effects compare to the synthetic hypoglycemic agents and because of their safety, effectiveness, and availability[9,11]. Although various synthetic drugs were developed to treat diabetes but still very less number of drugs is available for the treatment of diabetes[11]. There are about 200 pure compounds from plant sources reported to show blood glucose lowering effect. The compounds may be alkaloids, carbohydrates, glycosides, flavonoids, steroids, terpenoids, peptides and amino acids, lipids, phenolics, glycopeptides and iridoids. Many anti–diabetic products of herbal origin are now available in the market. More than 1 200 species of plants have been screened for activity on the basis of ethnomedicinal uses[7].

The ethnobotanical information reports a huge number of plants that may possess anti–diabetic potential, of which *Momordica charantia* (*M. charantia*), *Pterocarpus marsupium* (*P. marsupium*), and *Trigonella foenum* (*T. foenum*) greacum have been reported to be beneficial for treatment of type 2 diabetes. Herbal treatments for diabetes have been used in patients with insulin dependent and non–insulin dependent diabetes, diabetic retinopathy, diabetic neuropathy etc. The families of plants with the most potent hypoglycaemic effects include Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae[19]. Here all the enlisted plants were pharmacologically tested in the alloxan induced diabetic rat's model system.

9.1. Acacia arabica

The chloroform extracts of *Acacia arabica* (Leguminosae) bark in diabetic rats at 250 and 500 mg/kg, *p.o.* for two weeks, significantly decreased the serum glucose level and restored total cholestrol (TC), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) level. Moreover chloroform extract of *Benincasa hispida* fruit,

Tinispora cordifolia stem, *Ocimum sanctum* (*O. sanctum*) areal parts and *Jatropha curcus* leaves were shown the similar effect in the diabetic rats[20].

9.2. Achyranthes rubrofusca

The aqueous and ethanolic extracts of *Achyranthes rubrofusca* (Amaranthaceae) leaves in diabetic rats were investigated for anti–diabetic activity. It decreased the blood glucose level significantly, pancreatic enzyme such as superoxide dismutase (SOD), catalase (CAT) and glutathione level were significantly increased in the treated group compared to control group. Further aqueous extract showed better result compared to the ethanolic extract[21].

9.3. Andrographis paniculata

The oral administration of ethanol extract of *Andrographis paniculata* (Acanthaceae) in diabetic rats at a dose of 100 and 200 mg/kg, *p.o.* for 30 days treatment, significantly decreased the blood glucose level. Further it restored TG, TC, phospholipids, glycosylated haemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), acid phosphatase (ACP) and alkaline phosphatase (ALP) level which indicates its anti–diabetic activity[22].

9.4. Argyriea cuneata

The anti–diabetic activities of ethanol extract of leaves of *Argyriea cuneata* (Convolvulaceae) in diabetic rats were investigated and found to have significant anti–diabetic as well as lipid lowering potential[23].

9.5. Barleria prionitis

Alcoholic extracts of leaf and root of *Barleria prionitis* (Acanthaceae) in diabetic rats at 200 mg/kg, *p.o.* for 14 days treatment, significantly decreased blood glucose and glycosylated hemoglobin level. Moreover serum insulin and liver glycogen level were significantly increased[24].

9.6. Capparis decidua

The aqueous and ethanolic extract of *Capparis decidua* (Capparaceae) stem in diabetic rats at 250 and 500 mg/kg, *p.o.* for 21 days treatment significantly decreased the blood glucose level which signified its anti–diabetic potential[25].

9.7. Cassia grandis

The aqueous and ethanolic extracts of *Cassia grandis* (Leguminosae) in diabetic rats at the dose level of 150 mg/kg, *p.o.* for ten days treatment, significantly decreased the blood glucose, TC, and TG level proving its anti–diabetic potential[26].

9.8. Ceriops decandra

The anti–diabetic activity of ethanolic extract of the leaves of *Ceriops decandra* (Rhizophoraceae) in diabetic rats at 30, 60, 120 mg/kg, *p.o.* for 30 days treatment were investigated. Extract treated group modulated all the parameters such as blood glucose, hemoglobin, liver glycogen and some carbohydrate metabolic enzymes. Further 120 mg/kg, *p.o.* dose level was found to be more significant compared to other tested dose level[27].

9.9. Colocasia esculenta

Ethanol extract of *Colocasia esculenta* (Araceae) in diabetic rats at at 400 mg/kg, *p.o.* for 14 day, significantly decreased the blood glucose level and prevented loss of body weight. It indicates its anti–diabetic potential[28].

9.10. Costus igneus

Ethanolic extracts of leaves of *Costus igneus* (Costaceae) extracts in diabetic albino rats showed significant reduction of blood glucose level and prevented body weight loss indicating its anti–diabetic potential[29].

9.11. Eucalyptus citriodora

Aqueous extract of *Eucalyptus citriodora* (Myrtaceae) leaf in diabetic rats at 250 and 500 mg/kg, *p.o.* for 21 days treatment, significantly reduced the blood glucose level which confirms its anti–diabetic potential[30].

9.12. Ficus bengalensis

The aqueous extract of *Ficus bengalensis* (*F. bengalensis*) (Moraceae) bark in both insulin dependent diabetes mellitus (IDDM) and Non–insulin dependent diabetes mellitus (NIDDM) rats at 1.25 g/kg, *p.o.* for 4 weeks, significantly decreased the plasma glucose and serum lipids level. It shows anti–diabetic potential of *F. bengalensis*[31].

9.13. Heinsia crinata

The ethanolic leaf extract of *Heinsia crinata* (Rubiaceae) in diabetic rats for 2 weeks, significantly reduced the fasting blood glucose levels. It indicates its anti–diabetic potential[32].

9.14. Helicteres isora

The antihyperglycemic and hypolipidemic activities of butanol and aqueous ethanol extracts of *Helicteres isora* (Sterculiaceae) root in diabetic rats at 250 mg/kg for 10 days treatment were investigated. Extract treated group showed decreased level of blood glucose, TC, TG and urea. Further histological examination showed the restoration of pancreatic islets, kidney glomeruli, and liver to its normal size and therefore signified its anti–diabetic potential[15].

9.15. Ipomoea reniformis

The ethanolic and aqueous extracts of stem of *Ipomoea reniformis* (*I. reniformis*) (Convolvulus) in diabetic rats at 300 and 600 mg/kg, *p.o.* for 12 days treatment, significantly decreased the blood glucose and lipid level. From the obtained data it was found that *I. reniformis* have significant anti–diabetic antihyperlipidaemic potential[33].

9.16. Juglans regia

Anti–diabetic effects of methanolic extract of *Juglans regia* (*J. regia*) (Juglandaceae) leaves was estimated in diabetic male wistar rats at 250 mg/kg and 500 mg/kg, *p.o.* for three weeks. *J. regia* significantly decreased the blood glucose, TG and TC level. Further it increased GPX, SOD and cell antibody level significantly and therefore signified its anti–diabetic potential[34].

9.17. Lantana aculeata

The anti–diabetic effect of ethanolic extract of the dried mature roots of *Lantana aculeata* (verbenaceae) in diabetic rats at 25, 50 and 100 mg/kg, *p.o.* for 30 days treatment, was assessed. The plant significantly reduced the blood glucose level. Further it decreased TC and TG level and increased insulin and glycogen concentration in a dose–dependent manner, justifying its anti–diabetic potential[35].

9.18. Limonia acidissima

Methanolic extract of *Limonia acidissima* (Rutaceae) in diabetic rats at 200 and 400 mg/kg, *p.o.* for 21 days treatment, significantly decreased the blood glucose and malondialdehyde (MDA) level. Further the activity of antioxidant enzymes such as SOD, CAT were found to be higher in treated group compared to the control group which show the anti–diabetic and antioxidant potential of the plant[36].

9.19. Luffa aegyptiaca

The alcoholic and aqueous extracts of *Luffa aegyptiaca* (Cucurbitaceae) in diabetic rats at 100 mg/kg, *p.o.* for 15 days treatment, significantly decrease the blood glucose of hyperglycemic rats which signifies its anti–diabetic potential[37].

9.20. Momordic charantia

Anti–hyperglycemic and anti–oxidative potential of aqueous extracts of *Momordic charantia* (*M. charantia*) (Cucurbitaceae) pulp in diabetic rats for 30 days treatment were investigated. *M. charantia* extract significantly decreased the blood glucose levels. Moreover all other parameter was significantly restored in the treated group compared to control group. Further similar activity was found with the *T. foenum graecum* extract treatment[38].

9.21. Mukia maderaspatana

The methenolic root extract of *Mukia maderaspatana* (Cucurbitaceae) in diabetic rats at a dose of 500 mg/kg, *p.o.* for 21 days treatment, significantly decreased the blood glucose, TC, TG, LDL, phospholipids and very–low density lipoprotein (VLDL) level. Further it decreased serum glutamate oxaloacetate transaminases (SGOT), serum glutamate pyruvate transamineses (SGPT), alkaline phosphateses (ALP) and increased total protein (TP) content significantly at tested dose level[39].

9.22. Nymphaea pubescens

The ethanolic extract of *Nymphaea pubescens* (Nymphaeaceae) in diabetic rats at 200 and 400 mg/kg, *p.o.* after 14 days treatment significantly reduced the blood glucose level. Further histopathological examination of pancreas revealed its regenerative potential corroborating its anti–diabetic potential[40].

9.23. Ocimum gratissimum

The methanolic extracts of *Ocimum gratissimum* (Lamiaceae) in diabetic Wister rats at 500 mg/kg, *p.o.* showed significant reduction of blood glucose level. Moreover methanolic extracts of *Ocimum americanum*, *O. sanctum* and *Ocimum basilicum* also showed similar effect in the diabetic rats, with maximum potential in case of *O. sanctum* compared to the other tested extracts[41].

9.24. Paspalum scrobiculatum

Aqueous and ethanolic extracts of *Paspalum scrobiculatum* (Poaceae) in diabetic rats at 250 and 500 mg/kg, *p.o.* for 15 days treatment, significantly reduced the blood glucose level and lipid parameters. Further extract treated group showed a significant increase in the liver glycogen contents and a significant decrease in glycated haemoglobin level. Moreover 500 mg/kg, *p.o.* dose level showed more significant anti–diabetic activity compared to the 250 mg/kg, *p.o.* dose level[42].

9.25. Phoenix dactylifera

The *Phoenix dactylifera* (*P. dactylifera*) (Arecaceae) leaf extract in diabetes Wistar rats at 100, 200, and 400 mg/kg, *p.o.* and its fractions at 50, 100, and 200 mg/kg, *p.o.* for 14 days treatment, significantly reduced blood glucose, TC, TG level and water intake but increased plasma insulin level significantly compare to control group. The data obtained from experiment showed that *P. dactylifera* have anti–diabetic potential[43].

9.26. Phyllanthus niruri

The methanol extract of aerial parts of *Phyllanthus niruri* (Euphorbiaceae) in diabetic rats significantly reduced the blood glucose, TC and TG in a dose–related manner. Moreover histological studies showed that extract had imparted cell regenerative power in drug treated group which boosted its anti–diabetic potential[44].

9.27. Phyllanthus simplex

Various fractions of *Phyllanthus simplex* (Euphorbiaceae) such as petroleum ether (200 and 400 mg/kg), ethyl acetate (100 and 200 mg/kg), methanol (125 and 250 mg/kg), water fraction (150 and 300 mg/kg) were investigated for their anti–diabetic potential. Methanol (125 and 250 mg/kg) and aqueous fractions (150 and 300 mg/kg) showed significant antihyperglycemic effect. The active fractions also restored the antioxidant enzymes levels in liver and kidney[45].

9.28. Pongamia pinnata

The standardized ethanolic extract of *Pongamia pinnata* (*P. pinnata*) (Fabaceae) in diabetic rats was tested for its anti–diabetic potential. After 21–day treatment it was found that *P. pinnata* Posseses significant anti–diabetic activity[46].

9.29. Solanum nigrum

Antihyperglycemic and hypolipidemic effects of aqueous leaf extracts of *Solanum nigrum* (*S. nigrum*) (Solanaceae) in diabetic rats at 200, 400 mg/kg b.w. for 21 days treatment were investigated. Extracts of *S. nigrum* significantly reduced the blood glucose and other lipid parameter. Similar effect was also found with *Musa* extract. These findings show the anti–diabetic potential of these two plants[47].

9.30. Sphenostylis stenocarpa

The methanolic extract of seeds of *Sphenostylis stenocarpa* (Leguminosae) in diabetic rats at the doses of 200, 400 and 600 mg/kg, *p.o.*, significantly reduced the blood glucose level. Moreover, 600 mg/kg, *p.o.* was found to be more significant compared to other tested dose level[48].

9.31. Tephrosia villosa

Ethanolic extract of leaves of *Tephrosia villosa* (Fabaceae) in diabetic rats at two different doses, showed significant reduction in the blood glucose level. Moreover histopathological examination of pancreas showed regenerative power and therefore signified its anti–diabetic potential[49].

9.32. Trigonella foenum–graecum

The anti–diabetic activity of ethanol extract of *Trigonella foenum–graecum* (Fabaceae) seeds in diabetic rats at 2 g/kg, 1 g/kg, 0.5 g/kg and 0.1 g/kg, *p.o.* was investigated and it was found to have significant blood glucose lowering capacity. Further among all the tested dose level, 1 g/kg, *p.o.* was found to be more significant comparing to other dose levels[50].

9.33. Triumfetta rhomboidea

Treatment with ethanolic extract of *Triumfetta rhomboidea* (*T. rhomboidea*) (Malvaceae) in diabetes rats at doses of 100, 200, and 400 mg/kg, *p.o.*, significantly decreased the blood glucose level in dose dependent manner. From the data it was found that *T. rhomboidea* has significant anti–diabetic potential[51].

9.34. Vaccinium arctostaphylos

The ethanolic extract of *Vaccinium arctostaphylos* (*V. arctostaphylos*) (Ericaceae) fruit in diabetic male rats for 3 weeks, significantly decreased the blood glucose and triglyceride level. However it increased the erythrocyte SOD, glutathione peroxidase, catalase activities and expression of GLUT–4 and INS genes. These findings indicates anti–diabetic potential of *V. arctostaphylos*[17].

9.35. Vernonia amygdalina

The anti–diabetic activity of the various combinations of metformin (50 mg/kg) and aqueous extracts of the leaves of *Vernonia amygdalina* (Asteraceae) (100 mg/kg) in diabetic rats were investigated. Extract and metformin at the ratios of 1:1 and 2:1 were given to both normoglycemic and diabetic. From the data it was found that, blood glucose level was decreased more significantly by the drug combination compared to the single treatment of the drug in the diabetic rats[52].

9.36. Zaleya decandra

Effect of ethanolic extract of *Zaleya decandra* (Aizoaceae) roots in diabetes rats at 200 mg/kg, *p.o.* for 15 days treatment, significantly restored the levels of glucose, TC, TG, TP, urea, creatinine, lipid peroxidation level, and antioxidant enzymes. Histopathological studies showed significant regenerative power in the extract treated group compared to the control group[8].

9.37. Zizyphus mauritiana

The petroleum ether and aqueous extract of *Zizyphus mauritiana* (Rhamnaceae) at 200 and 400 mg/kg, *p.o.* doses, significantly restored the elevated biochemical parameters such as glucose, urea, creatinine, TC, TG, HDL, LDL, hemoglobin, and glycosylated hemoglobin. From the obtained data it was found that this plant had significant anti–diabetic potential[53].

10. Discussion

Diabetes mellitus is a chronic metabolic disorder of carbohydrates, proteins and fat metabolism which can be due to absolute or relative deficiency of insulin secretion or insulin resistance. It is characterised by high blood glucose level, which can cause various type of secondary complication associated with morbidity and mortality. The number of people suffering with diabetes worldwide is increasing at an alarming rate. It is predicated that, the number of diabetes person could reach upto 366 million by the year 2030[54]. Diabetes mellitus can cause both acute and chronic complications, resulting in blindness, kidney failure, heart disease, stroke and amputations. A proper treatment strategy is necessary to maintain glycemic control with proper excercise. Varieties of new pharmacologic treatments have been developed in the past 5 years to treat diabetes mellitus along with strategies dealing to diet management and exercise. There are mainly two categories of drugs available in the market for the treatment of diabetes mellitus, *i.e.* insulin and oral hypoglycemic agents[55]. Diabetic ketoacidosis is another serious metabolic complication associated with diabetes, which includes triad of hyperglycemia, metabolic acidosis, and increased ketone bodies concentration in the body. Due to coexistence of diabetic ketoacidosis and gestational diabetes mellitus chances of fetal loss increases many fold. From the data available in the litreature, it was found that, there is an explosive increase in the number of people diagnosed with diabetes mellitus worldwide in the last two decades. Type 2 diabetes, which is associated with modern lifestyle, abundant nutrient supply, reduced physical activity, and obesity makes main chunk of diabetic patients. Most number of type 2 diabetes complications are associated with obesity. Numerous studies have shown that insulin resistance precedes the development of hyperglycemia in subjects that eventually develop type 2 diabetes[3]. Diabetes mellitus is the biggest health care issue in North America and individuals having diabetes are at high risk of heart disease and other complications[56,57]. Oxidative stress can be an underlying cause of many diseases, such as diabetes mellitus. It can act through development of insulin resistance, β –cell dysfunction, impaired glucose tolerance, and mitochondrial dysfunction resulting in diabetic mellitus. Experimental and clinical data suggest that, chronic exposure to oxidative stress activates a series of stress pathways which can also cause diabetes mellitus[58]. There are numbers of tests for the diagnosis of the diabetic people, such as fasting blood glucose measurment, oral glucose tolerance test, and glycated hemoglobin[59–62].

Many numbers of animal models have been developed and described for the screening of anti–diabetic drugs. But none of them is exactly equivalent to human diabetes, but each model acts as essential tool for investigating genetic, endocrine, metabolic, morphologic changes and underlying aetiopathogenic mechanisms that could be associated with the development of diabetes[14]. Both alloxan and streptozotocin induced diabetes model is used as screening methods for anti–diabetic drugs. ROS in the cases of alloxan and DNA alkylation in the cases of streptozotocin mediate the toxic action. Due to chemical nature and greater stability, streptozotocin is mainly used for the reproducible induction of diabetes in experimental animals[55]. For the screening of anti–diabetic drugs, oral glucose tolerance test, streptozotocin or alloxan–induced diabetic animal models are used. There are various types of mechanisms associated with anti–diabetic activity of the compounds, which may be related to pancreatic –cells (synthesis, release, cell regeneration) or the increase in the protective effect against insulinase enzyme. Other involved mechanisms may be increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen and decrease of glycogenolysis, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates[19].

Medicinal plants that are effective in controlling plasma glucose level with minimal side effects are commonly used in developing countries as alternative therapy for the treatment of diabetes mellitus. In Africa, hundreds of plants are used traditionally for the management of diabetes mellitus, but only a few of such medicinal plants have been scientifically validated[54,63]. Currently available therapies for diabetes such as oral hypoglycemic agents and insulin have some side effects. A variety of chemical constituents present in medicinal plants can act on variety of targets by various modes and mechanisms, which can treat various acute and some chronic complication of diabetes[64]. Though anti–diabetic plants belong to diverse groups of families but most of them have been identified with some specific families such as Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae, which have significant impact on diabetes mellitus. Plant belongs in these family such as *Opuntia streptacantha*, *T. foenum graecum*, *M. charantia*, *F. bengalensis*, *Polygala senega* and *Gymnema sylvestre* have been shown to possess significant anti–diabetic potential[19]. Natural products classified into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown anti–diabetic potential through various type of modes of action. In the present review, plants which have shown anti–diabetic activity in alloxan induced diabetic rat have been included, among all of them *M. charantia*, *P. marsupium* and *T. foenum greacum* have been reported to have significant effect on diabetes mellitus[65].

In conclusion, this paper has presented the brief idea about diabetes and its related complication, epidimeolgy, diagnostic parameters, available therapies and plants having anti–diabetic potential tested in the alloxan–induced diabetic rat model. It showed that these plants have hypoglycaemic effects. In some cases they showed more significant anti–diabetic activity compared to the standard drugs. However lots of investigations is needed for the evaluation of mechanism of action of medicinal

plants with antidiabetic activity. Every plant material is not safe, therefore the toxic effect of these plants should be investigated before consumption. The less popularity of the herbal medicine in the modern medical practices is because of lack of scientific and clinical data, which provide its efficacy and safety. So for the safety point of view there is a need of conducting clinical research for herbal drugs. Developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation are also needed for the scientific validation of herbal drugs. It is also important to isolate and test the active components from the available plant extracts to get better treatment options compared to the traditional methods, which can be used for the treatment of various type of disorder including diabetes mellitus.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

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