REVIEW

Medicinal plants and management of Diabetes Mellitus: A review

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Abstract: Diabetes is a metabolic disorder characterized by chronic hyperglycemia and associated with dysfunction and failure of various body organs. Alarming increase in prevalence rate has made this disorder a major health problem globally. The available treatment modalities are not sufficient to combat diabetes and associated complications. A number of medicinal plants have a significant antidiabetic potential against diabetes mellitus. We have listed the use of important medicinal herbs for the treatment and management of diabetes in this review.

Keywords: Diabetes mellitus, diabetic complications, metabolic disorder, medicinal plants.

INTRODUCTION

Diabetes mellitus is a metabolic disorder that causes a disturbance in the metabolism, which leads to increase the glucose concentration outside the cell as a result of the resistance of insulin function or its secretion or decrease production by the pancreatic beta cells. Diabetes causes complications such as heart problems, eye problems, kidney function loss or other serious problems. Symptoms occur as a result of abnormality especially in the metabolism of protein, carbohydrates and lipids, which causes complications. Diabetes is a major health problem that results in reduced life quality and increased morbidity (Wei *et al.*, 2000; Ajani *et al.*, 2000).

In most previous studies, dietary and lifestyle factors increase the incidence of diabetes mellitus. Due to the disturbed metabolism of protein, fat and carbohydrate, an abnormal condition occurs in the body. Most common manifestations of diabetes are polydipsia, polyphagia and polyuria. In the same way, the common complications caused by the diabetes are cardiovascular diseases, kidney diseases and eye diseases, Dyslipidemia, hypoinsulinemia and hyperglycemia are the major characteristic of diabetes mellitus. Diabetes is usually managed with proper exercise, in which the excessive glucose is utilized by the body tissues, by avoiding the glucose-rich diet and oral hypoglycemic agents which maintain the glucose concentration at a certain level (Mallick *et al.*, 2007). About 10% cases of this disease occur most often in the American population and 2 million populations are affected by this disease in whole Europe and North America (Shamima *et al.*, 2013).

Prevalence of diabetes

Recently a report from World Health Organization (Shamima *et al.*, 2013) proposed that diabetes incidence is highest in India ranging to 32 million populations and this highest incidence will become three times more severe in coming 10 to 20 years than the current percentage. In developed countries, the prevalence of diabetes type 1 usually accounts for 90% both in adults and children. Like other countries, diabetes also affects the U.S population and its complications are the major cause of death in U.S population (Spanakis and Golden, 2013). Now a day, its prevalence is high as compared to previous studies in U. S population. Like other developing countries, diabetes mellitus has become a serious health problem for U. S population with no discrimination of sex. Incoming 10 to 20 years, the burden of diabetes and most commonly

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affected people will be between the age of 45 to 60 year despite the developed countries have the lowest rate and most commonly the victim of diabetes is above 65 year (Wild *et al.,* 2004).

According to the national survey, the highest prevalence of diabetes mellitus occurs in the capital of Iran (Tehran) (Azizi *et al.,* 2002). In Bahrain, the prevalence of diabetes is 23% that is more than the Iranian population instead of the fact that this country is a neighboring to Iran. Oman is another neighboring country to Iran but it has the lowest rate of diabetes prevalence (11.6%) estimated in 2000 (Al-Moosa *et al.,* 2006). The study showed that this prevalence of diabetes is more in the inner-city population (almost 17%) than the countryside population (10%) and most probably due to shifting towards the modernization and less physical activity and increase consumption of fatty food. The disease prevalence and incidence are greatly different in different countries like the children of Finland have a greater incidence of disease than the children of Venezuela. Prevalence of diabetes is increasing 3% annually. This increase in the disease burden is believed to be caused by the number of factors such as gene defect and the environment. Viruses play a vital role; most dominant are enteroviruses (Van *et al.,* 2014) rotavirus (*Honeyman et al., 2000*) and rubella. They make the immune system vulnerable to develop diabetes in young age (*Peltola, 2000, Gale, 2002*).

In western countries, the infants have no pathogens exposure or rare exposure to microbes that contribute to the development of diabetes. In 2000, a number of diabetes cases were 171 million. This incidence is 11% higher than the previous estimate of study. Recently World Health organization establishes the data that a number of deaths due to diabetes mellitus was 987,000 in 2002 that is 1.7% of total population of World. In 2000, it is estimated that there are 170 million people with diabetes worldwide (Wild *et al.,* 2004). This is a burden on the developing countries especially in poor countries and this burden may become double in coming years (Wild *et al.,* 2004).

Among the most populous countries of the world, only the Bangladesh and Nigeria have less number of diabetic cases and instead of these countries, Mexico, and Germany had the highest number of diabetes cases in 2010. Of course, there is a marked difference in the prevalence of diabetes in developed and developing countries. Developed countries have only 20% prevalence of diabetes and this disease affects most commonly aged people above the 60 years (Roy *et al.,* 2013).

Pathogenesis

Diabetes mellitus is mainly of two types, type I and type II. Type 1 is a complaint in which it is believed that destruction of the beta cell occurs and this leads to the absolute deficiency of insulin secretion (Devendra, 2004; Redondo, 2001; Abiru *et al.,* 2002). The environmental factors and food play a significant role in the development of diabetes in such a way that these factors change the cell-mediated immunity by the destruction of the beta cell (Robles and Eisenbarth, 2001; Helgason, 1981).

These cells cause abnormality in T cells activation in individuals who are already susceptible to diabetes and initiate the inflammatory process. As a result of the inflammatory process, antibodies and antigen produce and destruction occurs in islet cells of the pancreas. Due to the destruction of beta cells, insulin secretion is lost and when insulin secretion level falls below the required level, type 1 diabetes develops. Type II diabetes is actually disturbance in the metabolism and is also influenced by the number of factors mainly by the two prominent defective ways that the pancreas decreases the secretion of insulin, or insulin is secreted normally but resistance develops in its action on the body tissue and this leads to the increased glucose level in the blood. Many factors play role in the resistance of insulin and a major factor is the genetics of a person, age, fat deposition or excessive glucose consumption (Weisberg *et al.,* 2003; Aldhahi and Hamdy, 2003). As a result of insulin resistance, the pancreatic beta cells start producing more and more amount of insulin. As a result of continuous resistance in the action of insulin and increased its concentration may lead to the decreased its production and ultimately the extracellular hyperglycemia (Singh *et al.,* 2014).

Signs & symptoms

Signs and symptoms of diabetes mellitus include polyuria, polydipsia, polyphagia, nocturnal enuresis, paresthesia, peripheral neuropathy, pruritis, vulvovaginitis, recurrent blurred vision, fatigue, weakness and often asymptomatic in type 2 diabetes mellitus (Goswami *et al.,* 2006; Callaghan *et al.,* 2012). Once the abnormality develops in the pancreatic beta cells, most of the time, it can never reverse. However, signs and symptom of diabetes can be controlled through various ways such as by the utilization of medicines, which may not treat the actual pathology but may prevent the progression of disease or disease complications.

A study conducted by Navin *et al.,* (2008) from 2001 to 2003 gives an estimate that most of the diagnosed cases of diabetes have the symptoms (skin infections, urinary tract infection, genital itching, disturbance in vision, confusion, fatigue, weight loss, polyuria, polydipsia). In the United Kingdom, the research study on the symptoms gives an estimate that almost 31% of the patient in the country have no known symptoms. Diabetes mellitus is a disease that affects almost all the body system and disturbs their normal function. Very commonly it affects the gastrointestinal track and disturbs the normal function of gastrointestinal pathways (Ohlsson *et al.,* 2006).

Acute complications

It is believed that the complications from diabetes such as albuminuria may progress to death in almost 50% of the patients. A patient with diabetes is 2 to 4 times more at the risk of developing cardiovascular diseases than the normal population. Ketoacidosis is also the complication of diabetes that leads to acidosis, dehydration, hyperosmolarity and dehydration. Ketoacidosis causes hypoperfusion of vital organs and this may complicate coagulation process and this ultimately leads to infarction of brain and myocardium. Hypokalemia is another complication of diabetes mellitus (Fox, 2004).

Chronic complications

Diabetic neuropathy is observed in later stages of diabetes mellitus. Microalbuminuria, severe ketoacidosis, cardiovascular disease and increased height are the risk factors for diabetic neuropathy. Macro-angiopathy, diabetic neuropathy or combinations of both are the cause of diabetic foot. Pathogenic factors include the occurrence of edema, loss of adipose tissue and decreased collagen deposition. Diabetic neuropathy is a multifunctional disorder that affects neuronal system throughout the body. Cardiovascular disorders are 2 to 4 times more in patients with diabetic patients than non-diabetic people. In the United Kingdom, cardiac complications from diabetes mellitus type 2 are more common than the type 1 diabetes. According to study, 250 million are affected by diabetes and have a risk of death from the complications of diabetes (Iciar *et al.*, 2014). It is believed that the diabetes mellitus increases the chance of liver ailments because diabetes mellitus has relation to non-alcoholic fatty liver diseases and these non-alcoholic liver diseases are the major contributor to the development of hepatic carcinoma and hepatic tissue destruction because it causes inflammatory reaction that causes irreversible death of liver tissues and consequently cirrhosis (Falck *et al.*, 2001; Cotrim *et al.*, 2000; Shimada *et al.*, 2002). Diabetes may develop severe complications such as microvascular changes, macrovascular changes pulmonary function disturbance and eye changes.

Diagnosis of diabetes

Various tests are performed for diagnosis of diabetes mellitus. Most common tools for diagnosis of diabetes mellitus are history and physical examinations. Diagnosis of diabetes is usually made by identifying the raised glucose level above the normal value. Glucose tolerance test is performed in the patients with diabetes. Random glucose test, fasting blood glucose level and urine analysis etc. is more important tests for identifying the condition of diabetes. Almost all patients with diabetes are advised to monitor their diabetic condition by testing the blood glucose level rather than the urine test. Although urine analysis is a reliable test for the diagnosis of diabetes but the blood glucose estimation is more accurate and most suitable monitoring for diabetes and recommended for all kind of patients of diabetes. Urine test for ketone bodies is an important test for the patient of diabetes especially of type 1 diabetes mellitus who have absolute insulin deficiency. If the ketone bodies are present in urine, this is indicative of complicated diabetes. Now with advancing technology and awareness about diabetes, self-monitoring of blood glucose level may decrease the burden of diabetes. In this way, the patient may periodically check his own blood glucose level so maintain the certain level of glucose and prevent the complications. Blood glucose level can be accurately measured by taking blood glucose at morning especially in a fasting condition that gives the accurate value. All tests are very much necessary for the treatment of diabetes and also for the severity of extent of complications but these tests provide no longer measurement of glucose for a longer duration. Now for the assessment of glucose for a longer duration, there is a new test that revolutionizes the detection of hyperglycemia that is protein combined with glucose (glycated protein) and hemoglobin (Inzucchi, 2012).

Treatment

Treatment of type-1 diabetes mellitus

Insulin is given to patients with type 1 diabetes mellitus. Insulin controls blood glucose level that prevents major complications that affect blood vessels, nerve pathways, eyes and kidney (Bolli, 2006).

Treatment of diabetes mellitus type 2

Diabetes mellitus can be treated by diet modification, insulin and oral hypoglycemic agents. Dietary modification is effective in 60% of patients with diabetes mellitus. The total daily requirement of calories should be decided which depends on the financial resources, occupation, weight, sex and age. The low caloric diet should be given to obese patients with diabetes mellitus. Dietary fibers should be increased. Dietary fibers can cause 10% reduction in fasting blood sugar and LDL cholesterol. Treatment of obese people with a diet low in refined and higher than in unrefined carbohydrate and restricted in total energy contents result in increased insulin sensitivity which is associated with a rapid fall in the blood glucose concentration in obese diabetic (Post *et al.*, 2012). Oral hypoglycemic drugs are valuable in the treatment of patients with type 2 diabetes mellitus (NIDDM) who fail to respond to simple dietary restrictions. Biguanides and sulphonylureas are commonly used in the treatment of diabetes mellitus. In addition to these drugs, other new drugs such as non-sulphonylureas, insulin stimulators and alpha-glucosidase inhibitors are used in diabetes.

Few biguanides and sulfonylureas are used in non-insulin dependent diabetes mellitus, but these drugs are not able to reduce glucose level to normal. Utilization of biguanides and sulphonylureas is limited by secondary

Table 1: Plants having antidiabetic potential

Sr#	Plant	Parts of Plant used	Common Names	Reference
1	*Cuminum nigrum*	Seeds	Jiraka	Kaleem *et al*., 2005
2	*Vinca rosea*	Roots and shoots	Madagascar, Periwinkle	Kaleem *et al*., 2005
3	*Piper nigrum*	Fruit	Black Pepper	Kaleem *et al*., 2005
4	*Lodoicea sechellarum*	Seeds and leaves	Double Coconut Palm	Akhtar *et al*., 2009
5	*Holarrhena antidysenterica*	Bark and Seeds	Bitter Oleander, Connessi Bark	Mana *et al.,* 2010
6	*Butea monosperma*	Flower and seeds	Flame of the forest and bastard teak	Akhtar *et al*., 2010
7	*Swertia chirayita*	Seeds	Clearing Nut Tree, Bitter Stick	Saxena *et al.,* 2007
8	*Pisidium guajaya*	Fruits and Leaf	Guava, lemon guava	Singh and Marar., 2011
9	*Syzgium cumini*	Seeds	Java plum, Jamun	Singh and Marar., 2011
10	*Rhus verniciflua*	Stem	Chinese lacquer tree	Kim *et al.,* 2011
11	*Gymnema sylvestre*	Leaves and roots	Periploca of the woods / Gudmar	Grijesh *et al.,* 2009
12	*Ixora coccinea*	Leaves, roots, stems and flowers	Jungle geranium, Cambodia: Kam rontea	Maniyar and Bhixavatimath, 2012
13	*Embelia ribes*	Fruits, root	False Black Pepper, White-flowered Embelia, Vidanga	Bhandaria *et al*., 2013
14	*Vernonia amygdalina*	Leafs	Bitter leaf	Gyang *et al*., 2005
15	*Euphorbia hirta*	Whole plant	Snake weed	Kumar *et al*., 2010
16	*Vaccinium angustifolium*	Fruit and leaf	Bilberry, whortleberry or European blueberry	Martineau *et al*., 2006
17	*Caesalpinia bonducella*	Seeds	Fever nut, Bonduc nut and Kankarej	Chakrabarti *et al*., 2005
18	*Coscinium fenestratum*	Stems	Tree turmeric, False calumba and Colombo weed	Shirwaikar *et al.,* 2005
19	*Paspalum scrobiculatum*	Leaves	Rice grass, bastard/ditch/koda grass	Jain *et al*., 2010
20	*Rubus ellipticus*	Fruits and roots	Yellow Himalayan raspberry	Sharma *et al*., 2011
21	*Dodonaea viscose*	Leaves	Hopbush, viraali	Akhtar *et al*., 2011
22	*Curcuma longa* L.	Rhizome	Turmeric, haldi	Sukandar *et al.,* 2010
23	*Murraya koenigii*	Leaves	Curry leaf	Kesari *et al*., 2005
24	*Cyperus rotundus*	Tuber	Nut grass, Nut sedge	Raut and Gaikwad, 2006
25	*Swietenia mahagoni*	Leaves	Mahogany, Madeira redwood	Panda *et al.,* 2010
26	*Coreopsis tinctoria*	Flower	Calliopsis, Golden coreopsis,	Cai *et al.,* 2016
27	*Momordica charantia*	Fruits and seeds	Bitter melon, Bitter gourd, Bitter squash, or balsam-pear	Chaturvedi, 2012
28	*Aegle marmelos*	leaf and callus extracts	Bael, Bengal Quince, Holy fruit tree	Arumugam *et al.,* 2008
29	*Gymnema sylvestre*	Leaves	Meshashringi, Gurmar, Merasingi	Singh *et al,* 2015
30	*Glycyrrhiza glabra*	Leaves and Shrub	Licorice, Mulhathi,	Singh *et al,* 2015

failure rates and associated adverse effects. Even insulin does not reinstate a permanent normal pattern of glucose homeostasis and carries an increased risk of hypoglycemia and atherogenesis. According to recommendations of World health organization, research on medicinal plants demands attention. Medicinal plants have no or fewer side effects (Luna and Feinglos, 2001).

Herbal anti-diabetic agents

Hypoglycemic activity of the *Cuminum nigrum* seeds (0.5 and 1.5g/kg) in normal and diabetic rabbits induced by alloxan indicated that *C. nigrum* possess significant hypoglycemic activity. In another study, the anti-hyperglycemic potential of *Vinca rosea* and *Piper nigrum* (aqueous extracts) showed that *V. rosea* and *P. nigrum* exhibit significant hypoglycemic effect in alloxan induced diabetic rats (Kaleem *et al.,* 2005; Aderibigbe *et al.,* 2001). In another study, the antihyperglycemic activity of *Mangifera indica* Linn. was investigated in glucose induced hyperglycemia, normoglycemic and streptozotocin-induced diabetic mice. The hypoglycemic condition was observed by aqueous extract in glucose induced hyperglycemic and normoglycemic mice. The study indicated that *M. indica* extract has anti-hyperglycemic potential.

Hypoglycemic activity of *Lodoicea sechellarum* Labill in normal and type 2 diabetic human volunteers was investigated in 2009. Significant hypoglycemic activity was exhibited by *L. sechellarum* Labill in diabetic and normal human volunteers. This hypoglycemic activity may be due to constituents present in a plant that stimulate the release of insulin from the pancreas of normal and diabetic human volunteers or may possess insulin-like constituents (Akhtar *et al.,* 2009). Akhtar *et al.,* (2002) investigated the anti-hyperglycemic potential of *Alpinia galanga* rhizome on blood glucose levels. Significant hypoglycemic activity was exhibited by aqueous and methanolic extracts of *A. galanga* in normal rabbits. The decrease in blood glucose level was not significant in alloxan-induced diabetic rabbits.

The anti-diabetic potential of *Holarrhena antidysenterica* (methanolic extract) in diabetes induced by streptozotocin in rabbits indicated that *H. antidysenterica* possess significant hypoglycemic activity at an oral dose of 250mg/kg body weight (Mana *et al.*, 2010). Akhtar *et al.*, (2010) investigated the efficacy of *Butea monosperma* on lipid profile and blood glucose in diabetic and normal human volunteers and lipid profiles in normal and diabetic human volunteers. Blood glucose level significantly reduced at oral doses of 1, 2, and 3 g of powdered *B. monospema*. Saxena *et al.,* (2007) reported the antihyperglycemic activity of *Swertia chirayita*. Ethanolic extract of *S. chirayita* was administered orally in male albino rats. Significant blood glucose level was decreased at a dose of 250mg/kg body weight. The anti-hyperglycemic potential of *B. monosperma* in diabetic and normal human indicated that *B. monosperma* exhibits significant hypoglycaemic activity (Naeem and Hassan, 2010). The methanolic and aqueous extracts of leaves of *Pisidium guajaya* and seeds of *Syzgium cumini* inhibit α-amylase while the stem of *Rhus verniciflua* investigated for inhibition of α-glucosidase shows that *R. verniciflua* stem has α-glucosidase inhibition activity. There are various other plants that have α-glucosidase inhibition and α-amylase activity and can be prescribed in the treatment of diabetes mellitus. The combination of acarbose, a synthetic oral antidiabetic agent and *Anogeissus leiocarpus* (African birch) extract have also an inhibitory effect on α-amylase and synergistic effect on α-glucosidase enzyme inhibition. In addition to the antidiabetic property, this combination also has antioxidant property so such plants also have vital in maintaining fertility in diabetic patients (Riaz *et al.*, 2015; Adefegha., *et al.*, 2016). Gonzalez *et al.,* (2016) used various extracts of *Myrcia* genus including *M. salicifolia*, *M. sphaerocarpa* and *M. speciosa* for their antidiabetic affect. It was investigated extracts of these plants have 90-500 times more inhibitory effect on α-glucosidase (IC_{50}= 0.7 to 4.1μg ml^{-1}) than acarbose and also showed α-amylase inhibition effect (IC50=6.1 to 29μg mL-1). Further examples of medicinal plants having anti-diabetic potential are given in table 1.

CONCLUSION

Diabetes is a metabolic disorder characterized by chronic hyperglycemia and associated with dysfunction and failure of various body organs. Rapid increase in the rate of this disorder created an alarming situation throughout the world. So a renewed interest in addition of decreasing blood glucose level by various medicinal plants, functional foods, modulating physiological effects in the inhibition of α-glucosidase and α-amylase are also under investigation. This review contains a list of many plants, which are used for both to reduce blood glucose level and to decrease its absorption by inhibiting the carbohydrate hydrolyzing enzymes.

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