Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Review Article

HERBAL SOLUTION FOR THE TREATMENT OF DIABETES MELLITUS

Aruna Devaraj R* and Nirmala Anbu Rani R
*Director, Natural Resource Management Centre, Kallipatty, Periyakulam, Theni District-625605, Tamilnadu, India
Email: snakearuna@yahoo.com

Received on: 15/12/11 Revised on: 23/01/12 Accepted on: 27/01/12

ABSTRACT
Diabetes mellitus is a metabolic cum vascular syndrome of multiple etiologies characterized by chronic hyperglycemia with malfunction of carbohydrate, fat and protein metabolism. Medical plants play an important role in the management of diabetes mellitus especially in developing countries. Many ethnobotanical surveys on medicinal plants used by the local population have been performed in different parts of the world. The large numbers of herbals have demonstrated the importance of medicinal plants in the treatment and management of complications associated with diabetes. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycaemic plants showed antidiabetic activity with more efficacy than oral hypoglycaemic agents used in clinical therapy. Further, medicinal plants are also expected to serve as natural storehouse of novel antidiabetic leads.
KEYWORDS: Diabetes mellitus, Antidiabetic, Medicinal Plants, Herbal therapy, Pharmacognosy

INTTRODUCTION

Diabetes mellitus is a situation arises due the defect in insulin secretion, insulin action or both leading to modification in both small blood vessels (microangiopathy) and large blood vessels (macroangiopathy). Diabetes is a chronic disease that causes serious health complications including renal failure with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction, heart disease, stroke, and blindness. Further, it is associated with long term complications that lead to failure or malfunction of organ like eyes, kidneys, nerves, heart and blood vessels (Table 1). It is a commonest endocrine disorder that affects more than 100 million people worldwide (about 6% of population) and in the next 10 years, it may affect about 5 times more people than it does now [1]. India has 19.4 million diabetes patients and the count is increasing day to day. It is the fourth leading cause of death in the most developed countries and there is substantial evidence that it is epidemic in many developing and newly industrialized nations. Studies have shown that thiazolidinedione sensitizers are effective in terms of glucose lowering as oral hypoglycaemic agents. Glycaemic lowering occurs without additional demands on depleted islet cell insulin reserves. On contrary, insulin secretion improves with the application of these agents. Furthermore, there is evidence from both pre-clinical and clinical studies that new herbal agents lower blood pressure, albuminuria, and lipid metabolism, and are directly related to insulin resistance itself [2].

Table 1: Major risk factors in diabetic patients

Risk factor	Goal/intervention
Cigarette smoking	Smoking cessation. Inquire about smoking status at least annually, counsel current smokers every visit, prescribe nicotine replacement cautiously
Hypertension	ADA/AHA, <130/85 mm Hg; National Kidney Foundation, <130/80 mm Hg.
Hyperlipidemia	Priorities: (1) LDL cholesterol <100 mg/dL; treat with satins and resins. (2) Triglycerides <200 mg/dL (aggressive, <125 mg/dL review alcohol. (3) HDL cholesterol >45 mg/dL; recommend exercise, weight loss& estrogen therapy (women)
Hyperglycemia	Target hemoglobin A1c <7% has been proven to reduce micro vascular complications, but <6% may be needed to prevent macro vascular complications
Weight	Body mass index <27provide nutrition and exercise counseling

Thiazolidenediones

Thiazolidenediones are new class of drugs, which are used as insulin sensitizers. They are PPARg agonists and augment normal insulin signaling mechanism. Thiazolidenediones stimulate glucose uptake, inhibit lipolysis and induce glycogen synthesis and genes involved in insulin signaling mechanisms. They reduce the production of ROS (Reactive Oxygen Species). Rosiglitazone and pioglitazone are thiazolidinedione drugs that increase muscle sensitivity to insulin, improve insulin secretion and promote glucose tolerance and thus slow the progression to Type II diabetes.

Herbal therapy

Plants provide a potential source of hypoglycemic drugs. Several medicinal plants have found potential use as hypoglycemic in the Indian System of Medicines, including Ayurveda and Siddha. Since antiquity, diabetes has been treated with plant medicines. Many Indian plants have been investigated for their beneficial use in different types of diabetes. Ethnobotanical studies of traditional herbal remedies used for diabetes around the world have identified more than 1,200 species of plants with hypoglycemic activity. A large number of traditional remedies dedicated to diabetes likely reflect the relative ease of diagnosing this disease sugar in the urine can be determined even in technology-poor societies. Traditional knowledge, derived empirically, is supported by scientific testing. Recent scientific investigation has confirmed the efficacy of many of these preparations, some of which are remarkably effective [3]. The use of herbs as hypoglycemic is a major avenue in Indian perspectives particularly for treating diabetes, which require to be explored more effectively as there are so many literatures available on these aspects. Traditional plant medicines are used through-out the world for a range of diabetic presentations. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost. Therefore, investigation on such agents from traditional medicinal plants has become more important[4].

Pterocarpus marsupium

Pterocarpus marsupium is the source of the Kino of the European pharmacopeas. The gum-resin looks like dried blood (Dragon's blood), much used in Indian medicine. This medicinal herb has been used in ayurvedic medicine for diabetes treatment for a long time. In clinical studies it has

been shown to provide a blood sugar balancing property. Epicatechin, a flavonoid extracted from the bark of this plant, protects the beta cells in the pancreas from damage that causes a reduction in insulin production. In studies involving rats, this herbal treatment for diabetes even showed promise in rejuvenating damaged beta cells in the pancreas. This is the only herb, or drug, with this potential. The flavonoid, (-) epicatechin, extracted from the bark of this plant has been shown to prevent alloxan-induced beta cell damage in rats. Both epicatechin and a crude alcohol extract of *Pterocarpus marsupium* have actually been shown to regenerate functional pancreatic beta cells [5].

Momordica charantia

Momordica charantia is a tropical vegetable widely cultivated in Asia, Africa and South America, and has been used extensively in folk medicine as a remedy for diabetes. Bitter melon has been used extensively in traditional medicine for the treatment of diabetes. Its blood sugar lowering capabilities has attracted diabetics to this herbal supplements for centuries. Charantin, one of the active ingredients in Bitter melon, has been shown to be a potent hypoglycemic agent. It has similar effects to many hypoglycemic drugs used in diabetes treatment. Momordica, another active ingredient, has insulin-like effects, further decreasing blood glucose levels. Due to the potent hypoglycemic effect this supplement should be taken with care when using medications to control diabetes. The blood sugar lowering action of the fresh juice or extract of the unripe fruit has been clearly established in both experimental and clinical studies. Bitter melon is composed of several compounds with confirmed anti-diabetic properties. Charantin, an alcoholic extract of the fruit, contains both b-sitosterol-D-glucoside and 5, 25-stigmastaadien-3-B-ol-D-glucoside in a 1:1 mixture[6]. In addition, a 17-amino-acid polypeptide, referred to as vegetable insulin, has been isolated from *Momordica* fruit, seeds, and seedlings. This polypeptide does not cross-react in immune assays for bovine insulin[7]. It is assumed that the polypeptide would not survive exposure to stomach acid; in fact, the studies that use this extract deliver it by injection. Charantin has been reported to have glucose-lowering activity in alloxan-treated rabbits, rabbits, rats, and cats[6]. However, other investigators report difficulty documenting the hypoglycemic effects of this constituent[8]. In pancreatectomized animals, the effect of *Momordica* was equivocal, but recent studies says that efficacy of bitter melon, in lowering blood sugar in animals with very little pancreatic reserve[9].

Gymnema sylvestre

Gymnema sylvestre has been called the "sugar killer" due to its ability to reduce sweet cravings. Gymnema helps the pancreas with insulin production in type 2 diabetics, and increases the sensitivity to insulin in type 1 diabetics. Some type 2 diabetics have been able to discontinue their use, or reduce their dosage, of oral diabetic medications with use of this supplement. *Gymnema* assists the pancreas in the production of insulin in Type II diabetes. *Gymnema* also improves the ability of insulin to lower blood sugar in both Type I and Type II diabetes. It decreases cravings for sweet. It is an excellent substitute for oral blood sugar-lowering drugs in Type II diabetes. Traditionally, the leaves are chewed whole, taken as a powder, or drunk as a water decoction[5]. Many constituents (gymnemic acids) have been isolated from *G. sylvestre* since nineteenth century for the treatment of diabetes Extract of Gymnema, GS4, contains more than 15 triterpene sapinoids (gymnemic acids) polypeptide, gurmarin. Pharmacologic actions of *Gymnema* have been studied in animal models. The plant has been able to normalize blood sugar in animals treated with agents that destroy beta-cell function but not in animals that have been pancreatectomized[10]. *Gymnema* in a water based extraction increased the effect of exogenous insulin in normal and hyperglycemic rats, and decreased the plasma glucose in mildly diabetic rats[11]. Powdered and water-based extracts from leaf stimulate insulin secretion in rats[3]. In-vitro and animal data suggest three possible physiologic mechanisms of actions for *Gymnema* (1) increased insulin secretion through action on the pancreas, (2) increased tissue sensitivity to insulin, and (3) decreased oral intake of calories due to an alteration in the sensation of taste. *Gymnema* is frequently included in Ayurvedic formulas for diabetes and is often used as a folk treatment for diabetes[12].

Trigonella foenum-graecum

Fenugreek has strong anti-diabetic properties, as well as triglyceride and LDL cholesterol lowering effects. It has also been shown to support HDL (good cholesterol) levels. Defatted fenugreek seed powder has been shown in studies to increase glucose tolerance and decrease fasting blood glucose levels after as few as 7 days. Experimental and clinical studies have demonstrated the antidiabetic properties of fenugreek seeds. The active ingredient responsible for the antidiabetic properties of fenugreek is in the defatted portion of the seed that contains the alkaloid trogonelline, nicotinic acid and coumarin. Fenugreek seeds have high fiber content, up to 50 percent; it is mucilaginous and rich in galactomannans. Trigonelline, an alkaloid derived from the metabolism of nicotinic acid, has been isolated from the seed and shown to have hypoglycemic effects[13]. Whole seeds have been shown to be hypoglycemic in normal and mildly diabetic animals but not in those with severe disease. Bailey and Day postulate that the high fiber content of fenugreek seeds decreases absorption of glucose by slowing transit time in the gut[8]. Defatted seeds lowered blood glucose as well as glucagon in dogs, both normal and diabetic. Trigonelline showed a weak and transitory hypoglycemic effect when given orally to diabetic patients, presumably by slowing the metabolism of nicotinic acid, a hyperglycemic constituent. In addition to its effects on glucose, fenugreek seed, especially the fiber component, lowers cholesterol and triglyceride levels in normal and diabetic animals and patients[14].

Other Indian medicinal plants with hypoglycemic activity

Since time immemorial, various plants and plant derived compounds have been used in the treatment of diabetes to control the blood sugar of the patients. The use of herbs in the management of diabetes mellitus has been prevalent in Indian society from a long time. Several medicinal plants have reported to possess potential hypoglycemic activity in Indian system of medicines. There have been several reviews on the hypoglycemic medical plants[15], more particularly use of Indian botanicals for hypoglycemic activity

MATERIALS AND METHODS

Study subjects

The study group (368 patients) comprised of diabetic subjects recruited who volunteered themselves for the programmed treatment and were then called as Herbal Respondents. A survey was conducted at Government Hospital, Periyakulam, Theni District, Tamilnadu, India to find out the nature of Diabetics mellitus prevalent in and around Theni District.

Collection of the Plant

The leaves of were collected from the wild in the Theni District, during the month of May- Jun 2011.

Preparation of the Extract

The dried leaves were subjected to successive extraction 5-8 by using different solvents of ascending polarity i.e. Petroleum ether, Butanol, Ethyl acetate and Ethanol in a Soxhlet apparatus. Aqueous extraction was carried out by maceration method.

Stage I

A preliminary study was carried out to assess their health status, age particulars, symptoms and track record of the disease. The question raised provided sufficient particulars for the stage II analysis of the urine and blood sugar. The following symptoms were recorded as diabetic syndrome – fatigue, diarrhea, increased thrust (polydipsia), increased hunger (polyphagia), frequent urination (polyurea), loss of weight and lethargy and lack of interest.

Stage II

Urine sugar, blood sugar, (fasting and postprandial) and the results were obtained from the herbal respondents who were selected as subjects in the present study.

Clinical and biochemical parameters

Clinical and biochemical parameters were followed by Standard methods such as age and duration of Diabetes were recorded and a complete clinical examination was done. Blood pressure was recorded in sitting position in the right arm to the nearest 2mm Hg with a mercury sphygmomanometer.

Body Mass Index

A frequent use of the BMI is to assess an individual's body weight departs from what is normal or desirable for a person height. The weight excess or deficiency may, in part, be accounted for by body fat (adipose tissue) although other factors such as muscularity also affect BMI significantly. WHO regard a BMI of less than 18.5 as underweight and may indicate malnutrition, an eating disorder, or other health problems, while a BMI greater than 25 is considered overweight and above 30 is considered obese. Body Mass Index (BMI) was calculated by the formula Weight in Kg/Height in m^2 (Kg/m^2), with the rating as in **Table 2.**

Table 2: Body Mass Index (BMI) Category

Category	BMI range – kg/m^2
Severely underweight	less than 16.0
Underweight	from 16.0 to 18.5
Normal	from 18.5 to 25
Overweight	from 25 to 30
Obese Class I	from 30 to 35
Obese Class II	from 35 to 40
Obese Class III	over 40

However BMI below 20 is known as underweight and a value of BMI above 25 is known as obese. Most of the obese patients suffer from diabetics after the age of 40. The study was carried out with Type II Obese patients. A fasting blood sample was collected after an overnight fast of at least 10 hours for biochemical investigations, which were carried out, on Corning Express Plus Auto analyzer (Corning, Medfield, MA, USA) using kits supplied by Boehringer Mannheim, Germany. Fasting and 2hr plasma glucose estimations (glucose oxidase method),

RESULTS AND DISCUSSION

Diabetes is the most common disorder associated with glucose metabolism. Diabetes is regarded as the major risk factor that leads to the development of many diseases and disorder in human system. It is the major factor that contributes to cardiac myopathy/cardiac hypertrophy. Diabetes is mostly associated with the change in the endogenous level of insulin. The clinical characteristics and biochemical features of the subjects used in this study are presented in Table 3. Based on the clinical characteristics features of the subjects it could be observed that age is a non significant criterion among the diabetic subjects. The values obtained for the diabetic subjects were almost similar and comparable to the normal are non diabetic subjects. Further, it could be inferred that diabetes can occur at any stage of development (age). Comparison of body mass in index of the subjects used in the study shows that there is no significant correlation between the diabetic and the non diabetic individuals. Hence body mass index is a non significant parameter. Statistical evaluation of the clinical data and the p value show that this factor has less influence on the onset of diabetics in the population.

Table 3: Clinical characteristics of the study subjects

Parameters	Non-diabetic subjects	Diabetic subjects
Age (years)	47.0 ± 7.0	50.0 ± 14.0
Duration (years)	5.0 ± 2.5	5.0 ± 2.5
Body mass index (Kg/m^2)	23.6 ± 6.4	26.4±5.3
Glycated hemoglobin (HbA1c) (%)	5.7 ± 0.4	8.3±2.5

It has been well established by several studies that glucose level is a key factor is used to differentiate diabetic subjects from normal individuals. Comparative analysis of fasting plasma glucose level indicates that it is almost twice in the diabetic patients (151.0 ± 60.0) as against the normal value of 84.0 ± 9.0 in the non diabetic individuals. Comparative analysis of the % glycated hemoglobin content among the diabetic and non diabetic individuals revealed that this parameter is also one of the significant factors that influence the onset of diabetics. It could be observed from the Table 3 that the normal level of % glycated hemoglobin content (5.7 ± 0.4) increased to 8.3 ± 2.5 in the diabetic subjects. Further statistical analysis of this parameter revealed that % glycated hemoglobin content is serves an indicator to diagnose of diabetics. The p value of 0.001 indicates that it is one of the key factors which could be used to determine the clinical manifestation of diabetic patients. Further, statistical evaluation of the data revealed that the p value for all the three variables were significant. Insulin exhibited a moderate activity. But metformin was found to be the least potent agent in reducing the peroxynitrite formation as indicated by their statistical analysis.

Herbal treatment for diabetes has been a part of traditional medicine for thousands of years. The natural herbs for diabetes treatment focus on lowering blood sugar and reducing the damaging effects of the disease. Herbal supplements for diabetes should be a part of a holistic approach to treatment that addresses proper nutrition, a good exercise program, and continued monitoring of blood glucose levels. It is important to visit a medical professional for proper diagnosis of diabetes and follow up treatment for the disease. After a diagnosis of diabetes it is important to continue follow up care and education to ensure the best treatment possible. Herbal remedy for diabetes containing a collection of medicinal herbs and other natural ingredients known to support pancreatic health, promote systemic balance and the healthy functioning of the Islets of Langerhans in the pancreas which is responsible for insulin production. Case study of a diabetic patients demonstrating positive effect due to herbal intervention is given in Table 4.

Table 4 Case study of a Diabetic patient demonstrating positive effect due to herbal intervention

Weight Kg	BP	Urine Sugar	Blood Sugar (Fasting) mg %	Blood Sugar (PP) mg %
62	130/90	3+	132	227
60	120/80	1+	135	177
62	120/80	nil	134	172
61	110/80	nil	129	156
62	120/80	2+	131	140
63	110/80	1+	127	139
61	110/80	1+	111	123
59	120/80	2+	115	127
54	110/80	2+	113	124
62	120/80	2+	111	129
60	110/80	2+	112	127
Allopathy + Herbal Therapy				
62	120/80	1+	102	127
61	110/80	1+	97	124
62	120/80	nil	97	129
63	110/80	nil	98	113
61	110/80	nil	99	125
Allopathy + Herbal Therapy + Yoga				
57	110/80	1+	99	120
Allopathy + Herbal Therapy + Yoga + Dietopathy				
62	120/80	1+	97	120
61	110/80	Trace	92	120

Table 5 Percentage inhibition of PMA induced ROS by insulin and insulin sensitizers

Test Agents	Control	Diabetes	p value
Troglitazone (10 mM)	68	39	0.004
Rosiglitazone (10 mM)	36	14	0.008
Pioglitazone (10 mM)	40	26	0.01
Metformin (10 mM)	16	8	NS
Insulin (30 nm)	38	11	0.004

Table 5 depicts the differential action of insulin and insulin sensitizers in reducing the formation of peroxynitrite in SIN-1 treated platelets. The peroxynitrite scavenging action of glitazones is in the order of pioglitazone > troglitazone > rosiglitazone with the p value of 0.01 > 0.004 > 0.008 respectively. It could be observed that insulin had a moderate effect and metformin exhibited the least effect on the removal of peroxynitrite in SIN-1 treated platelets. In all the three cases the treatment had a comparable effect. However, when compared to control subjects (non diabetic individuals), the % reduction in peroxynitrite generation due to glitazones was significantly ($p<0.05$) lower in platelets from Type II diabetes subjects. The resistance to peroxynitrite generation by insulin was also significantly lower in diabetic patients. But Metformin had no significant effect on the % reduction in peroxynitrite generation in both the control subjects (non diabetic individuals) and platelets from Type II diabetes subjects.

In diabetic subjects, PMA-induced ROS generation was positively correlated with HbA1c values and was found to statistically significantly ($r=0.6$; $p=0.01$). Multiple linear regression analysis revealed that PMA-induced ROS generation functioned as dependent variable and BMI, HbA1c, serum cholesterol, triglyceride, HDL, systolic and diastolic blood pressure as independent variables. However, after adjusting for age and sex, only HbA1c levels a positive correlation ($\beta=0.623$, $p<0.001$) with increased PMA-induced ROS generation was observed. These observations clearly indicate that parameters such as age and sex were not statically significant. Therefore care must be taken in the choice of the drug for the treatment of diabetics and the duration of the treatment must be taken into account so as to avoid cardiac complications arising out of it. The effectiveness of the drug used in the treatment of diabetes thus depends on the complications associated with the development and progression of the disease. More recently herbal remedies have gained due prominence in the treatment of diabetics. However the usage of the preparation made out the herbs differ largely in their usage and practice across different alternative systems of medicine used for the treatment of diabetes. Moreover these studies await scientific conformation and clinical efficacy before launched into the public domain Herbal treatment for diabetes has been a part of traditional medicine for thousands of years[16]. The natural herbs for diabetes treatment focus on lowering blood sugar and reducing the damaging effects of the disease. Herbal supplements for diabetes should be a part of a holistic approach to treatment that addresses proper nutrition, a good exercise program, and continued monitoring of blood glucose levels.

CONCLUSION

Diabetes is a metabolic disorder with chronic complications. In order to check this health problem, development of novel hypoglycaemic and antidiabetic agents is of great interest. Many new bioactive drugs from plant sources have significant antidiabetic activity sometimes on par or even

more than known oral hypoglycaemic agents. However, plant based drugs have not been well characterized therefore scientific investigations are of want.

REFERENCES

1. ADA Clinical Practice recommendation, screening for diabetes Diabetes Care 1997; 20(1): 22-24
2. King H, Aubert RE, Herman WH (1998) Global burden of diabetes,1995-2025 Prevalence, numerical estimates and projection Diabetes Care 21:1414-1431
3. Shanmugasundaram ER, Gopinath KL (1990). Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Ethnopharmacol 30:265-279.
4. Suba V, Murugesan T, Arunachalam G, Mandal S., Saha BP (2004a) Anti-diabetic potential of Barleria lupulina extract in rats Phytomedicine 11:202–205
5. Dash VB (1987). Materia medica of Indo-Tibetan medicine. MDIA Classics India Publications, ND.
6. Marles RJ, Farnsworth NR (1995). Antidiabetic plants and their active constituents. Phytomedicine 2(2):137-189.
7. Zafar R, Neerja N (1991). Momordica charantia - A review Hamdard Medicus 34(3):49-61.
8. Bailey CJ, Day C (1989). Traditional plant medicines as treatments for diabetes. Diabetes Care 12(8):553-564.
9. Raman A, Lau C (1996). Anti-diabetic properties and phytochemistry of Momordica charantia. Phytomedicine 2(4):349-362.
10. Prakash AO, Mathur S, Mathur R (1986). Effect of feeding Gymnema sylvestre leaves on blood glucose in beryllium nitrate treated rats. J Ethnopharmacol 18:143-146.
11. Chattopadhyay RR, Medda C, Das S (1993). Hypoglycemic and anti hyperglycemic effect of Gymnema sylvestre leaf extract in rats. Fitoterapia 64(5):450-454.
12. Khajuria S, Thomas J (1992). Traditional Indian beliefs about the dietary management of diabetes - An exploratory study of the implications for the management of Gujarati diabetics in Britain. J Hum Nutr Diet 5(5):311-321.
13. Jain SC, Agrawal M, Sharma RA (1996). The genus Trigonella—Phytochemistry and biology. Ancient Sci Life. XVI:108-117.
14. Indian Council for Medical Research (ICMR) (1987). Role of fenugreek seeds in diabetes mellitus. ICMR Bulletin 17(9):79–93.
15. Ivorra MD, Payaa M, Villarb A, (1989) A review of natural products and plants as potential hypoglycemic drugs J Ethnopharmacology 27:243-275
16. Bnouham M, Ziyyat A, Mekhfi H, Tahri A, Legssyer A (2006) Medicinal plants with potential antidiabetic activity - A review of ten years of herbal medicine research (1990-2000) Int J Diabetes & Metabolism 14: 1-25