DIABETES MANAGEMENT : THE THERAPEUTIC ROLE OF AYURVEDIC HERBS

Muhammed Majeed Ph.D. & Lakshmi Prakash Ph.D.
Sabinsa Corporation, 70, Ethel Road West, Unit 6, Piscataway,
New Jersey 08854, United States of America

Abstract:

Diabetes has become a leading killer disease in recent years and its prevalence is a "basic health indicator" for member states of the World Health Organization.
The preponderance of Type II diabetes is attributed to an increase in obesity and lack of physical activity in populations with enhanced standard of living. This article reviews the use of Ayurvedic herbs in diabetes management, in the context of current advances in medical and scientific research.

Diabetes mellitus, commonly known as diabetes, is one of the world's oldest known diseases. In 1997, diabetes prevalence was introduced as a "basic health indicator" for member states by the WHO, which estimated in 1995 that the number of people with diabetes in the world would reach 300 million by 2025. About 16 million people suffer from diabetes in the US alone, with an estimated 120 million sufferers worldwide. A recent publication by the WHO links 3.2 million deaths worldwide to diabetes, each year [1]. Type II diabetes accounts for most of these cases. The Center for Disease Control in the United States (CDC) attributes the phenomenal increase in diabetes cases to the growing prevalence of obesity and decline in physical activity. According to a recent report presented by the Center, one in three Americans born in the year 2000 will develop diabetes [2].

Diabetes mellitus is caused either by a lack of the hormone insulin (Type I diabetes) or the body's inability to use insulin (Type II diabetes also known as maturity-onset diabetes). Type II diabetes is often triggered by obesity, stress and a sedentary lifestyle.

Type I, also called juvenile onset diabetes or insulin dependent diabetes mellitus (IDDM) accounts for about 10% of the total cases of the disease and afflicts the sufferers quite early in life. IDDM is caused by an individual's inability to make insulin. Type II or maturity onset diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), accounts for almost 90% of the diabetes cases. It is associated with a defect in insulin secretion as well as insulin resistance. Individuals who are abdominally obese (central obesity) tend to have diminished capacity to utilize glucose. They also have high levels of circulating free fatty acids (which impair glucose metabolism) and a low number of insulin receptor sites[4]. Recent studies point towards genetic predisposition to the disease which is more widely prevalent in certain ethnic groups including Native

Americans, Hispanics, African Americans and Asian Americans in the US. A study on Mexican –Americans revealed that the presence of specific variations in one gene resulted in a three fold increase in the risk of diabetes. Calpain-10 a protein associated with this gene has been shown to be involved in glucose regulation[5]. A third type of diabetes called gestational diabetes is known to occur in some women in the last trimester of pregnancy and persists after delivery.

Depending upon the nature of the disease, insulin and certain synthetic drugs like sulphonylureas, biguanidines and acarbose are widely used in its treatment. Before the discovery of insulin by Frederick Banting and Charles Best in 1921, patients with severe cases of diabetes did not survive. Today, although seldom fatal, diabetes is a dreaded disease on account of the related complications. Careful management of diabetes, including control of high blood pressure, can delay some of the serious complications associated with the condition, which include eye diseases, disease of the peripheral blood vessels and kidney failure[3,6]. In recent years, evidence of cases of "insulin resistance" and the occurrence of side effects from prolonged administration of conventional drugs have triggered the search for safe and effective alternatives. Several plant extracts and isolated phytochemicals have been examined for anti-diabetic activity with a view to identify alternative treatment strategies for diabetes. It has been observed that certain resistant cases of diabetes that do not respond well to conventional drugs often respond well to supplementation with natural remedies.

Diabetes is a chronic disorder characterized by high blood sugar levels and abnormal metabolism of carbohydrate, protein and fat. The disease is a result of the failure of the body to control blood sugar levels adequately. The normal fasting blood sugar levels are in the range of 75-115 mg/dL (milligrams per deciliter of blood). After a meal, the body tightly regulates increases in blood sugar to a level not exceeding 180 mg/dL in people without diabetes.

In a normal person, food which is made up of protein, carbohydrate and fat is digested by the enzymes in the digestive tract. Glucose, a simple sugar is an important end product of digestion. It is absorbed into the bloodstream and transported to the various cells in the body where it is utilized as a fuel to provide energy for the various life activities. Insulin is a hormone which acts as a key that opens the doors of the cells to allow glucose to enter. Insulin is produced in the body by beta cells, specialized cells located in the islets of Langerhans of the pancreas. The islets of Langerhans contain three types of cells that help in glucose metabolism: alpha cells which make glucagon; beta cells which produce insulin ; and delta cells which secrete somatostatin, a hormone which regulates the production of insulin and glucagon. Normally, insulin and glucagon regulate blood glucose levels, causing almost all carbohydrate and about 50 to 60

percent of protein to be converted into glucose. Glucose is consumed as fuel by almost every type of body cell.

In a person suffering from type I diabetes there is an insufficient or no supply of insulin. In type II diabetes, insulin may be present in sufficient quantities, but it is unable to unlock the doors of the cells. In the normal case, insulin "fits" on to specific sites called insulin receptors located on the surface of the cell (the key holes) and unlocks the "doors" to let glucose enter. If the insulin cannot fit in properly due to lack of insulin receptors on the cell surface, the "doors" remain locked, causing a condition called insulin resistance. In such cases of diabetes, administration of insulin does not help because there are few receptor sites. If the doors of the cells remain unopened, due to lack of insulin or difficulty in utilizing insulin, glucose cannot enter the cells and remains in the blood. This causes increases in blood sugar levels even if no food is eaten. Urine sugar levels increase when some of the excess blood sugar is excreted. The body begins to use alternative fuel sources (e.g. body fat and protein) for energy. The patient therefore loses weight, tires easily and has an increased appetite (polyphagia).

Excess glucose in the blood is harmful too. Sugar accumulation in the blood results in increased workload on the kidneys and increased sugar levels in the urine. The sugar enters the urine in solution form, draining water from the cells. This causes an increase in the volume of urine which triggers frequent urination (polyuria), and induces thirst (polydipsia) in the patient. High blood sugar levels over protracted periods of time causes "glycation" of key body proteins inducing secondary symptoms such as retinopathy which may lead to blindness, neuropathy (nerve degeneration) which may lead to gangrene, and nephropathy which may lead to kidney malfunctions[3,6].

Current approaches to diabetes management

Diet control and exercise:

Lifestyle management including diet control and adequate exercise is essential to the successful treatment of Type II diabetes. Experts on diet and health and the American Diabetes Association (ADA) state that there is no single dietary regimen for diabetes. Dietary recommendations may be developed based on the individual's requirements and treatment goals. Successful nutritional management of diabetes entails[7]:

- Regular monitoring of metabolic parameters (including blood glucose, glycated hemoglobin, lipids, and blood pressure)
- Maintaining healthy body weight
- Lifestyle management

It is important that diabetics space meals adequately over the day to avoid glucose overload and low blood sugar. The daily dietary caloric breakdown recommended states that 12-20% of the total calories should be supplied by protein, less than 10% of the total calories should be from saturated fats and up to 10% of the calories from polyunsaturated fats and 60-70% of the total calories to be distributed between monounsaturated fats and carbohydrates, based on individual requirements.

Complex carbohydrates, such as those from whole grains and vegetables are advocated because they have a lower glycemic index. The glycemic index represents the sugar value of the food as compared to glucose given a value of 100. All carbohydrates are ultimately converted to glucose in the body. Some nutritionists use white bread as the standard, in which case white bread would have a glycemic index of 100 and glucose would have an index of 142. The lower the glycemic index, the slower the carbohydrate would convert to glucose, thereby avoiding glucose overload.

In view of the increased risk of cardiovascular disease, diabetics should avoid saturated fats (limit to less than 10% of dietary fat) and limit daily cholesterol intake to less than 300 mg. A diet containing adequate fiber is recommended and is beneficial in maintaining healthy cholesterol levels and gastrointestinal health. Current guidelines advocate a daily intake of 20-35 g per day.

For people with mild to moderate hypertension, 2,400 mg or less per day of sodium is recommended. For people with hypertension and nephropathy, 2,000 mg or less per day of sodium is recommended. Mild to moderate weight loss (5-10 kg [10-20 pounds]) has been shown to improve diabetes control, even if desirable body weight is not achieved. NIDDM patients are recommended physical exercise in order to support cardiovascular health, inhibit obesity and augment nutritional measures.

Therapeutic measures

The aim of therapy is to maintain blood glucose at normal levels. Drug therapy includes glucose lowering agents as well as medications to treat or prevent the secondary complications of the disease. In Type II, an additional impairment to the success of insulin therapy is insulin resistance. In normal individuals, the structure of insulin fits onto specific receptors on the surfaces of cells in muscle, liver and adipose tissue. The processes underlying glucose metabolism are triggered when insulin interlocks with these receptors. In insulin resistant individuals, however, this mechanism is hampered. In such cases, insulin may be produced adequately, but cannot be utilized effectively.

In the conventional treatment of Type II, sulphonylureas, biguanidines or acarbose are orally administered, singly or in combination, as adjuncts to dietary therapeutic measures. Most of them act by increasing insulin secretion or by inhibiting glucose synthesis in the liver. The sulphonylureas sensitize the beta cells to glucose, resulting in enhanced endogenous insulin secretion. The glucose production in the liver is simultaneously suppressed, and may lead to hypoglycemia in some individuals who are on reduced calorie intake or are prone to general debility, renal impairment or alcohol consumption. The biguanides prevent the synthesis of glucose in the liver, thereby reducing blood sugar levels. There may also be a mild reduction in intestinal glucose absorption. However, there may be high levels of lactic acid produced, resulting in lactic acidosis and gastrointestinal disturbances. Biguanides are contraindicated in patients with renal impairment, hepatic dysfunction and cardiac failure. Acarbose is a competitive inhibitor of intestinal alpha-glucosidases and acts by delaying carbohydrate digestion and slowing down carbohydrate absorption. However, the side effects include digestive disturbances due to impaired absorption of carbohydrates. A new drug, Troglitazone, has now been developed with a view to reducing insulin resistance. This drug is used singly or in combination with sulphonylureas[6].

The Ayurvedic approach to diabetes:

Ayurveda, the ancient healing system from India, has steadily increased in popularity in the western world in recent years. This 5,000 year old system of medicine recommends a combination of lifestyle management (which includes diet, exercise and meditation), and treatment with specific herbs and minerals to cure various diseases. The botanicals in the Ayurvedic materia medica have been proven to be safe and effective, through several hundred to several thousand years of use.

Ayurvedic physicians have treated diabetes for thousands of years using a combination of regulated lifestyle and herbal formulations. The following paragraphs summarizing the description of diabetes mellitus by two ancient Indian physicians, are excerpted here from a fairly recent publication on Ayurveda[8]:

"About the one transmitted genetically, he (Sushruta) says " *a person would be diabetic if his father and grandfather are diabetic*". In fact, he mentions that such type of person is clinically diabetic. The genetically transmitted entity of insulin dependent diabetes mellitus is well known today. What is striking, is his description of an insulin dependent diabetic whom he describes as a thin, restless individual. The characteristics of diabetes of dietary origin are described to be

exactly opposite, which also fit in with the features of Type II mentioned in modern medicine.

Charaka too agrees with the genetic origin of diabetes and adds that this type is more difficult to cure. The ancient physicians have written factors predisposing to diabetes mellitus, and these stand confirmed even today. The factors described are lack of exercise, sedentary habits, sleeping during day time and eating excessively, particularly sweet and fatty substances. these individuals lack enthusiasm, are overweight, obese and have excessive appetite."

These physicians also prescribed specific herbal formulations for the treatment of diabetes. Some of these herbs, with a record of safety and efficacy, spanning several centuries, are described in the following pages. In recent times, the safety and efficacy of these herbs have been validated by laboratory experiments and clinical trials.

Ayurvedic herbs for the management of diabetes

***Gymnema sylvestre* (Australian Cow Plant)**

The leaves of this plant (referred to in the vernacular as "gur mar" meaning "sugar destroyer"), belonging to the botanical family Asclepidaceae have the property of abolishing the taste of sugar. Laboratory studies suggest that water extracts from the leaves help in improving sugar assimilation in animal models of diabetes. The active principles include a glycoside mixture, the gymnemic acids and a peptide, gurmarin, both of which inhibit the sweet taste response in mammals. In traditional medicine, the plant is used either singly or in combination with other Ayurvedic herbs. The blood sugar lowering effects of the leaf extracts were further confirmed by researchers who found that damaged islets of langerhans in diabetic rats could be regenerated by administration of GS_4, a standardized extract obtained from *Gymnema sylvestre* leaves[9]. This led to the hypothesis that *Gymnema* extracts could induce the pancreas to secrete insulin[10], a finding confirmed by later laboratory experiments and clinical studies on Type I and Type II diabetes patients [11-13].

***Momordica charantia* (Bitter melon)**

The fruits of the plant are well known in Ayurvedic medicine and in folk use as being useful in diabetes management. Laboratory experiments and clinical trials using an extract of the dried fruits from the plant indicate that it lowers blood sugar levels[14-16]. Although the precise mechanism of action remains to be fully determined, *Momordica charantia* is a proven hypoglycemic agent.

In controlled clinical studies, *Momordica charantia* extracts have been shown to significantly lower blood sugar levels, particularly in patients with Type II diabetes. In view of these effects, *Momordica charantia* is a potential herbal alternative in diabetes management, particularly in non-insulin dependent diabetes[17,18].

***Trigonella foenum graecum* (Fenugreek)**

A member of the Leguminosae family, the seeds of this commonly used spice contain about 50 percent fiber, of which 20 percent is mucilaginous fiber similar to guar gum, which is a known hypoglycemic agent. The protein fraction of the seeds contains the amino acid 4-hydroxyleucine which has been proven to stimulate insulin production[19]. Saponins present in fenugreek seeds have also been shown to lower cholesterol levels in human subjects[20].

Recent studies have revealed the efficacy of defatted fenugreek seed extracts in the management of both Type I and Type II diabetes[21-24]. Administration of defatted fenugreek seed powder for a period of three weeks significantly improved the performance of Type II diabetes patients in the glucose tolerance test. Additional beneficial effects included lowered urinary sugar and reduced serum cholesterol levels. Some of the patients under treatment also reduced their insulin requirements from 56 units per day to 20 units per day. This effect was found to be sustained and lasting with no undesirable side effects. Within the duration of this study, there were no new incidences of heart problems such as angina and myocardial infarction and no increases in blood pressure, indicating that fenugreek may be helpful in preventing the secondary complications of diabetes such as hyperlipidemia and atherosclerosis.

***Pterocarpus marsupium* (Vijayasar)**

Pterocarpus marsupium Roxb. (from the family Leguminosae) known in the vernacular as "Vijayasar" of "Bijasar" is a large tree that commonly grows in the central, western, and southern parts of India and in Sri Lanka. It is known as "kino" for the dried exudates obtained by incising the trunk. The heartwood, a durable and termite resistant material, has been used traditionally in the management of diabetes and hyperlipidemia.

Pterocarpus marsupium is a rich source of polyphenolic compounds. The key compounds include the diaryl propane derivative, propterol; the stilbene, pterostilbene; the hydrochalcone, pterosupin; the benzofuranone, marsupsin; the flavanoid, liquiritigenin and the catechin, (-)-epicatechin. Of these, the compounds pterostilbene and (-) epicatechin are reported to have blood sugar lowering effects in laboratory studies[25]. (-)-Epicatechin has also been shown to have an effect on the conversion of proinsulin to insulin[26]. *P. marsupium*, alone or as in multi-ingredient formulations, has also been successful in reducing the blood sugar of diabetic humans. In one laboratory study, pancreatic beta-

cell regeneration was observed in alloxan-induced diabetic rats that received the flavonoid fraction from the bark of *P. marsupium*[27].

The Indian Council of Medical Research undertook an anti-diabetic Phase II open trial at four centers across India using Vijayasar. Vijayasar was tested in newly-diagnosed non-insulin dependent diabetes mellitus (NIDDM) patients between 35 and 60 years of age for 12 weeks. Ninety-three of 223 patients admitted for the therapy were evaluated for 12 weeks[28]. Patients responded well to the therapy with no untoward side effects. Another clinical study with 20 participants also reported beneficial effects on the symptoms of diabetes[29].

Salacia species (Salacia oblonga, Salacia reticulata) **(Pitika)**

One of the conventional therapeutic approaches to diabetes management is through the use of alpha-glucosidase inhibitors that lower glucose levels by blocking the enzymes that digest starches in the intestines. This results in delayed absorption of complex sugars and a lowering of blood sugar after a meal. Several constituents[30,31] of a botanical extract obtained from the dried roots of *Salacia reticulata* (family Celastraceae, known as Vairi or Pitika in Sanskrit) were found to inhibit alpha-glucosidase enzymes in a similar manner.

Investigations on the effects of an aqueous extract prepared from the stems of *S. reticulata* extract (SRE) on postprandial hyperglycemia in rats and humans revealed that SRE suppressed an increase in serum glucose levels when fed with sucrose, maltose, and starch but not glucose or lactose in a dose-dependent manner. In the sucrose tolerance test conducted on human volunteers, administration of 200 mg p.o. SRE 5 minutes before sucrose loading (50 g) significantly suppressed postprandial hyperglycemia. Double blind placebo controlled trials on human volunteers with mild Type II diabetes showed promising results[32, 32(a)].

Ocimum sanctum **(Tulsi, Holy basil)**

This plant, used in Ayurveda for over 2000 years has now been explored as an adjunct to dietary therapy and drug treatment in mild to moderate Type II diabetes. Results of a single-blind placebo-controlled trial indicated a significant decrease in blood glucose levels during the treatment of Type II diabetes with Tulsi leaves as compared to placebo[33].

Tinospora cordifolia **(Guduchi)**

The beneficial effects of this plant in diabetes management are well documented in traditional medicine. Recent research reveals that these effects observed in animal models can be attributed to the bitter principle isolated from the water extract. This principle has been shown to enhance insulin

secretion and improve glucose metabolism , thereby lowering blood sugar levels[34].

Szygium cumini (***Eugenia jambolana***)

The fruit kernels of this plant (Java plum, "jamun") have are used traditionally in the management of diabetes. Studies on animal models revealed that extracts from the plant promote insulin secretion in isolated islets of Langerhans and lower blood sugar levels in experimental diabetes[35,36]. The whole fruit powder is traditionally used in mixed formulations for diabetes management.

Another herb with potential blood sugar lowering activity is *Coleus forskohlii*. Forskolin, the active component in the plant extract, is a direct activator of adenylate cyclase and raises the levels of cyclic-adenosine monophosphate (cAMP). It is an effective anti-hypertensive agent. Preclinical studies revealed that forskolin at the 10mM level potentiated glucose-induced insulin release in vivo as well as in the perfused rat pancreatic islet system. This finding is important to people predisposed to diabetes or those suffering from Type II diabetes. Forskolin could help in glucose metabolism by improving the body's utilization of insulin[37].

A water extract of the common culinary spice, cinnamon is reported to enhance glucose metabolism and to provide insulin-like action[55]. Cinnamon is used as a "balancing" herb in Ayurvedic formulations, benefiting metabolic processes. Other Ayurvedic herbals with potential blood sugar lowering activity include *Vinca rosea* Linn (documented *in vitro* studies are available)[38]; *Caesaria esculanta* (studies on the anti-diabetic effects in rabbits are available)[39]; *Ficus bengalensis*[40] (a leucodelphidin derivative isolated from this plant showed 20% glucose level reduction in normal rats); *Coccinia indica*[41] (studies on experimental animals have been performed), *Cyamopsis tetragonolobus*[42] (fruit extract and seeds (containing guar gum) effective in experimental animals), *Bougainvillea spectabilis* (alcoholic extract contains pinitol which is an effective hypoglycemic agent in experimental animals)[43], *Azadirachta indica* (neem)[44] (which has proven hypoglycemic action in rats and rabbits), *Aegle marmelos* and *Hibiscus rosa sinensis* (which showed hypoglycemic action in rats)[45].

<u>Scientific basis for using mixed formulations :</u>

Ayurvedic remedies for diabetes are usually mixed formulations[46,47] containing blood sugar lowering herbs in combination with immunomodulators, diuretics and detoxicants. The rationale behind such formulations is provided by modern research, which documents that immune processes play a predominant role in the destruction of beta cells and that free radicals[48] feature predominantly in the progression of the disease and its secondary complications. The inclusion

of immunomodulators, and detoxifying antioxidants in mixed formulations is therefore beneficial. Some traditional formulations also contain cholesterol-reducing agents and adaptogens such as *Emblica officinalis*.

Weight reduction would be beneficial to the sensitivity of the receptor cells to insulin, in cases of obesity-induced insulin resistance. More recent studies provide the link between obesity and the development of Type 2 diabetes. Researchers identified a mechanism that helps explain how the hormone leptin (originally termed the "satiety signal"), is involved in the metabolism of fatty acids in muscle.[51] A novel molecular link between obesity and diabetes is thus indicated, suggesting the possibility of a new target for the development of drugs that would help manage both conditions. The potential applications of nutraceuticals in this context cannot be ruled out. For instance, recent studies suggest that *Garcinia cambogia* extract efficiently improved glucose metabolism and displayed leptin-like activity in mice.[52] *Garcinia cambogia* extract (more accurately, its active compound (-) hydroxycitric acid) is a well known dietary supplement that supports weight loss and healthy body composition. In view of the significance of obesity in the etiology of Type II diabetes, inclusion of herbs such as *Garcinia cambogia*[49] that support weight management may be beneficial if used in combination with conventional drugs such as metformin[50].

Vascular inflammation is now regarded by medical researchers as the key underlying cause for several chronic disease conditions, including diabetes [53]. On a related note, recent research reveals that diabetes raises the risk of gum disease (an inflammatory condition), and the risk of some types of cancer [54].

Anti-inflammatory approaches such as Turmeric root (contains curcuminoids that help in inhibiting COX-2 enzymes), *Commiphora mukul* (Guggul) extract (contains guggulsterones and ferulates that help in reducing markers of inflammation such as C-reactive protein [CRP] in the plasma), and other healthful medicinal plants from Ayurveda, are therefore integrated into diabetes support formulations. These healthful herbs also support cardiovascular health through their beneficial effects against vascular inflammation.

A comprehensive Ayurvedic therapeutic regimen thus offers time tested safe and effective support to conventional therapy in the management of diabetes. This in combination with adequate nutritional support (consisting of a well balanced diet and supplemental vitamins and minerals, including trace minerals such as selenium, chromium, vanadium in bioavailable forms), and lifestyle management would provide an integrated approach to the management of diabetes, particularly Type II diabetes.

References:

1. Unwin, N. and Marlin, A. (2004) Diabetes Action Now: WHO and IDF working together to raise awareness worldwide; 49(2): 27-31.
2. http://www.diabetes.org/for-media/scientific-sessions/06-14-03-2.jsp, accessed March 15, 2005.
3. Nathan, D.M. (1997). ***Diabetes***. The General Hospital Corporation.
4. Kissebah, A.H. et al. (1995). Central obesity and free fatty acid metabolism. ***Prostagland. Leucotrien. Ess. Fatty Acids***, 52:209-211.
5. Sreenan, S.K. et al. (2001) Calpains play a role in insulin secretion and action. ***Diabetes*** 50(9):2013-20.
6. Campbell, R.K. (1997) Type II Diabetes Mellitus : Disease State Management. ***Retail Pharmacy News***, October : 15-18.
7. General information on diabetes **http://www.diabetes.org, http://www.diabetesnet.com**
8. Dahanukar, S. and Thatte., U. (1989) Ayurveda Revisited. Popular Prakashan, Bombay, 12.
9. Shanmugasundaram, E.R.B. et al. (1990) Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given ***Gymnema sylvestre*** leaf extracts. ***J. Ethnopharmacology*** 30: 265-279.
10. Shanmugasundaram, K.R. et al. (1981) The insulinotropic activity of ***Gymnema sylvestre*** R. Br., an Indian medicinal herb used in controlling diabetes mellitus. Pharmacological Research Communications, 13:475-486.
11. Srivatsava, Y. et al. (1985) Hypoglycemic and life-prolonging properties of ***Gymnema sylvestre*** extract in diabetic rats. ***Israel J. Med. Sci.*** 21:540-542.
12. Shanmugasundaram, E.R.B. et al. (1990) Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. ***J. Ethnopharmacology***, 30:281-294.
13. Baskaran, K. et al. (1990). Anti-diabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. ***J. Ethnopharmacology*** 30, 295-300.
14. Leatherdale, B.A. et al. (1981) Improvement in glucose tolerance due to *Momordica charantia* ***British Medical Journal***, 282:1823-1824.
15. Srivastava, Y. et al. (1993). Anti-diabetic and adaptogenic properties of Momordica charantia extract: an experimental and clinical evaluation. ***Phytotherapy Res.***, 7(4), 285-289.
16. Sarkar, S. et al. (1996) Demonstration of the hypoglycemic action of Momordica charantia in a validated animal model of diabetes. ***Pharmacological Research***, 33(1):1-4.
17. Raman A and Lau C. (1996) Anti-diabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). ***Phytomedicine***, 2(4), 349-362,.
18. Welihinda, J. et al. (1986) Effect of *Momordica charantia* on the glucose tolerance in maturity onset diabetes. ***J. Ethnopharmacology*** 17:277-282.
19. Sauvaire, Y. et al. (1996) Steroid saponins from fenugreek and some of their biological properties. ***Advances in Experimental Medicine & Biology***, 405:37.
20. M AL-Habori and A Raman. (1998) Antidiabetic and hypocholesterolaemic effects of fenugreek ***Phytotherapy Research***, 12, 233-242.
21. Sharma, R.D. (1986) Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses. ***Nutrition Research***, 6: 1353-1364.
22. Sharma, R.D. et al. (1990) Effect of fenugreek seeds on blood glucose and serum lipids in Type I diabetes. ***Eur. J. Clin. Nutr.*** 44 : 301-306.
23. Sharma, R.D. et al. (1990). Hypoglycemic effect of fenugreek seeds in non-insulin dependent diabetic subjects. ***Nutrition Research***, 10:731-739.

24. Sharma, R.D. et al. (1996) Hypolipidemic effect of fenugreek seeds. ***Phytotherapy Res***. 10: 332-334.
25. Manickam, M., et al. (1997) Antihyperglycemic activity of phenolics from *Pterocarpus marsupium*. ***J. Nat. Prod***., 60(6), 609-610.
26. Ahmad, F., et al. (1991) Effect of (-) epicatechin on cAMP content, insulin release and conversion of proinsulin to insulin in immature and mature rat islets in vitro. ***Ind. J. Exp. Biol***. 29, 516-520.
27. Chakravarthy, B.K., et al. (1980) Pancreatic beta-cell regeneration- a novel antidiabetic mechanism of *Pterocarpus marsupium*, ROXB. ***Ind. J. Pharmacol***., 12(2), 123-127.
28. Indian Council of Medical Research (ICMR) Collaborating Centres, Central Biostatistical Monitoring Unit, Chennai & Central Technical Coordinating Unit, ICMR, New Delhi (1998) Flexible dose open trial of Vijayasar in cases of newly-diagnosed non-insulin-dependent diabetes mellitus. ***Ind. J. Med. Res***., 108, 24-29.
29. Ojha, J.K., et al. (1978) Hypoglycemic effect of *Pterocarpus marsupium* Roxb (Vijayasar). ***J. Res. Ind. Med. Yoga & Homoeo.,*** 13, 4.
30. Yoshikawa, M., et al. (2001) Polyphenol constituents from Salacia species: quantitative analysis of mangiferin with alpha-glucosidase and aldose reductase inhibitory ***Yakugaku Zasshi***. 121(5):371-8.
31. Yoshikawa, M. et al. (1998) Kotalanol, a potent alpha-glucosidase inhibitor with thiosugar sulfonium sulfate structure, from antidiabetic ayurvedic medicine *Salacia reticulata* ***Chem Pharm Bull (***Tokyo). 46(8):1339-40.
32. Kajimoto, O. et al. (2000) Effect of Diet Containing Salacia reticulata on Mild Type 2 Diabetes in Humans -A Placebo-controlled, Cross-over Trial ***J. Jpn. Soc. Nutr. Food Sci***. 53(5):199-206.
32. (a) Heacock PM et al. (2005) Effects of a medical food containing an herbal alpha-glucosidase inhibitor on postprandial glycemia and insulinemia in healthy adults. ***J Am Diet Assoc***.; 105(1):65-71.
33. Chattopadhyay, R.R. (1993) Hypoglycemic effect of Ocimum sanctum leaf extract in normal and streptozotocin diabetic rats. ***Indian J. of Exp. Biol.,*** Vol. 31,891-893.
34. Gupta, S.S.et.al. (1967) Anti-diabetic effects of *Tinospora cordifolia*. ***Ind. J. Med. Res***.Vol. 55(7), 733-744.
35. Kedar, P. and Chakrabarti, C.H. (1983) Effects of jambilan seed treatment on blood sugar, lipids and urea in streptozotocin induced diabetes in rabbits. ***Ind. J. Physiol. Pharmac***. 27(2):135-141.
36. Achrekar S et al. (1991) Hypoglycemic activity of *Eugenia jambolana* and *Ficus bengalensis*: mechanism of action. ***In vivo***. 5(2):143-147.
37. Ammon, H.P. T. et al. (1985) Forskolin : From an Ayurvedic remedy to a modern agent. ***Planta Medica***. Vol 51, 475-476.
38. Chattopadhyay, R.R. et al (1991) Hypoglycemic and antihyperglycemic effect of the leaves of *Vinca rosea* Linn. ***Indian J. Physiol. Pharmacol.*** 35(3):145-151.
39. Gupta, S.S et al. (1967) Studies on the anti-diabetic effects of *Caesearia esculenta*. ***Ind. J. Med. Res.*** 55(7):754-763.
40. Geetha, B.S. and Mathew, B.C. (1994). Hypoglycemic effects of leucodelphidin derivative isolated from *Ficus bengalensis*. ***Indian J. Physiol. Pharmacol***. 38(3):220-222.
41. Singh, N. et al. (1985). A study on the anti-diabetic activity of *Coccinia indica* in dogs. ***Ind. J. Med. Sci.*** 39:27-29.
42. Pillai, N.R. et al. (1980) Hypoglycemic effect of *Cyamopsis tetragonoloba*. ***Indian J. Med. Res***. 72:128-137.
43. Narayanan, C.R. et al., (1987) Pinitol - A new anti-diabetic compound from Bougainvillea spectabilis leaves ***Current Science***, Vol. 56(3),139-141.
44. Chattopadhyay RR. (1999) A comparative evaluation of some blood sugar lowering agents of plant origin***. J Ethnopharmacol*** 67(3):367-72

45. Sachdewa, A. et al. (2001) Effect of *Aegle marmelos* and *Hibiscus rosa sinensis* leaf extract on glucose tolerance in glucose induced hyperglycemic rats (Charles foster). ***J Environ Biol*** 22(1):53-57
46. Yajnik, V.H. et al. (1993). Efficacy and safety of D-400, a herbal formulation, in diabetic patients ***The Indian Practitioner***, Vol. XLVI (12), 917-922.
47. Nair, R.B. etal. (1992) Antidiabetic activity of Amrithadi churnam. ***Ancient Science of Life***, Vol. No. XII Nos 1 & 2, 280-85.
48. Oberley, L.W. (1988) Free radicals and diabetes. ***Free Radical Biol. Med***. 5:113-124.
49. Hackman, R. (1996). Insulin resistance : Nutritional and herbal solutions. ***Nutrition Science News***, May issue, 37.
50. McCarty MF (1998) Utility of metformin as an adjunct to hydroxycitrate/carnitine for reducing body fat in diabetics.***Med Hypotheses*** 51(5):399-403
51. Yasuhiko, M. et al. (2002) Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature 415: 339 – 343.
52. Hayamizu K et al. (2003) Effect of *Garcinia cambogia* extract on serum leptin and insulin in mice. Fitoterapia. 74(3):267-73.
53. Vinik, AI (2004) Inflammation: The Root of all Evil in Diabetes and the Dysmetabolic Syndrome. http://www.medscape.com/viewarticle/496269; accessed March 15, 2005.
54. Ujpal, M. et al. (2004) Diabetes and Oral Tumors in Hungary. ***Diabetes Care.*** 27:770-774.
55. Khan A, et al. (2003) Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care; 26(12):3215-8.