A FUSION OF ANCIENT MEDICINAL PLANTS WITH MODERN CONVENTIONAL THERAPIES ON ITS MULTIFACETED ANTDIABETIC PROPERTIES

*** Susmit Kosta, and Archana Tiwari**

School of Biotechnology, Rajiv Gandhi Proudyogiki Vishwavidyalaya (University of Technology of Madhya Pradesh), Bhopal, 462036, India.

** E-mail: skosta@aol.in*

Summary

Ayurveda, the ancient healing system from India, has steadily increased in popularity in the western world in recent years. This 5,000 years 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. This review summarizing the description of diabetes mellitus by two ancient Indian physicians are excerpted here from a fairly recent publication on Ayurveda: “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. In recent times, the safety and efficacy of these herbs have been validated by laboratory experiments and clinical trials

Keywords: Non-insulin dependent diabetes mellitus, Reactive oxygen specie, Antioxidant, Lipid peroxidation

Introduction

Diabetes is defined as a condition that occurs because of lack of insulin or presence of factors opposing the action of insulin resulting in an increase (hyperglycemia) in blood glucose levels poor control of diabetes leads to complication which could damage small blood vessels throughout the body, thereby causing impaired delivery of nutrients and hormones to the tissues and eventually causing tissue- damage several tissue could be affected[1]. It usually leads to a series of late complication for example vascular complication. Vascular complication caused by endothelial cell dysfunction. Recently increasing evidence suggests the formation of free radicals is involved in the pathogenesis of diabetes and the development of diabetic complication[2]. The oxidative stress is significantly increased in diabetes because prolonged exposure to hyperglycemia increase the generation of free radicals and reduce capacities of the antioxidant defense system[3]. A free radicals result in the consumption of antioxidant defense which may lead to disruption of cellular functions and oxidative damage to membranes and enhance susceptibility to lipid peroxidation (LP). Increased generation of reactive oxygen specie (ROS) and (LP) has been found to be involved in the pathogenesis of many disease of know and unknown etiology and in the toxic actions of many compound[4]. Antioxidants thus play an important role to protect the human body against damage caused by reactive oxygen species[5]. The endogenous antioxidant enzyme (eg. SOD, CAT, GSH and GPX) are responsible for the detoxification of delicious oxygen radicals, Diabetes is the leading cause of blindness in people ages 25 to 74, damages nerves, kidneys, the heart and blood vessels and may result in the amputation of limbs[6,39].

In diabetes as blood glucose level increases, the body cannot metabolize this excess glucose in a normal way (Figure 1). Increased glucose is metabolized by other abnormal pathways are: (i) Glucose gets converted into sorbitol. (ii) Conversion into advance glycosylation end products. (iii) Glucose gets oxidized and gets converted to free radicals. (iv) Activation of protein kinase C[7].

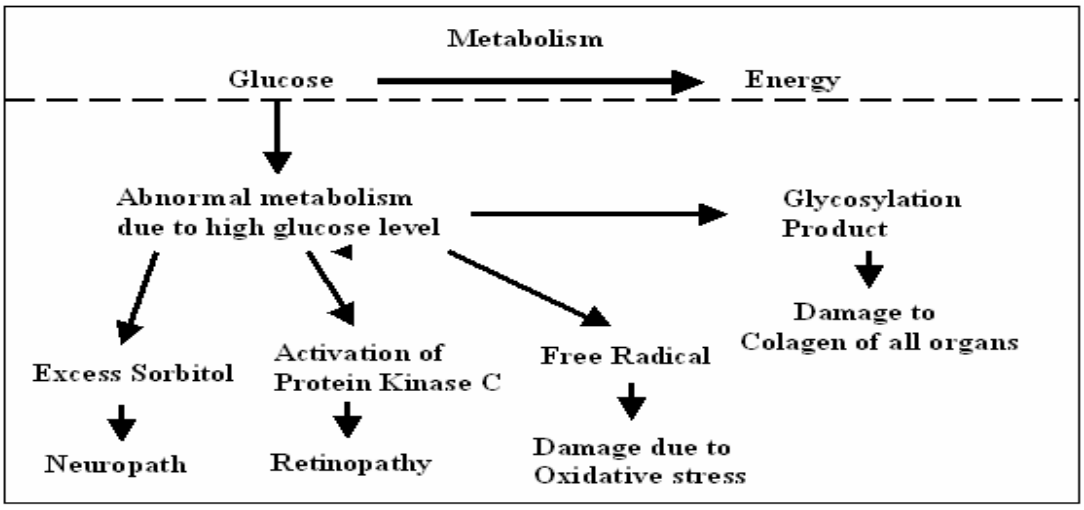

Figure 1. Normal and abnormal metabolism of glucose

The metabolism of glucose by these alternate pathways leads to production of a number of metabolites and chemicals, which are harmful to various body organs. The damage to various body organs by diabetes is called diabetic complications. These may occur as a result of damage to small vessels (microangiopathy) or large vessels (macroangiopathy). Bad effect of diabetes on body occurs due to high glucose since metabolism of this excess glucose takes place through abnormal pathways leading to accumulation of toxic metabolites. If glucose level is kept in normal range then these complications can be prevented [8].

Conventional Therapies

The general consensus on treatment of type 2 diabetes is that lifestyle management is at the forefront of therapy options. In addition to exercise, weight control, and medical nutrition therapy, oral glucose-lowering drugs and injections of insulin are the conventional therapies. Since the most important pathological process during the development of diabetes involves three key organs, i.e., pancreatic islets, liver, and skeletal muscle, almost all anti-diabetic therapies are aimed at these organs. Pharmacological treatment is indicated when fasting glucose level exceeds 140 mg/dL, the postprandial glucose level exceeds 160 mg/dL or HbA1c exceeds 8.0 percent.[9,10].

Pharmacological Treatment and Limitations

Oral Glucose-Lowering Drugs:

In the United States, five classes of oral agents are approved for the treatment of type 2 diabetes. By conventional standards, oral therapy is indicated in any patient with type 2 diabetes in whom diet and exercise fail to achieve acceptable glycemic control[10]. Although initial responses may be good, oral hypoglycemic drugs may lose their effectiveness in a significant percentage of patients. The drug categories include sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides. Sulfonylureas, including first generation (e.g., tolbutamide) and second generation (e.g., glyburide) sulfonylureas, enhance insulin secretion from the pancreatic beta-cells. A significant side effect is hypoglycemia. Sulfonylurea therapy is also usually associated with weight gain due to hyperinsulinemia,[11,12] which has been implicated as a cause of secondary drug failure[10,12].

Biguanides include the drug metformin, which was originally derived from a medicinal plant, Galega officinalis. Metformin reduces plasma glucose via inhibition of hepatic glucose production and increase of muscle glucose uptake. It also reduces plasma triglyceride and LDL-cholesterol levels. Side effects include weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity. Alpha-glucosidase inhibitors include the drug acarbose. This drug category decreases postprandial glucose levels by interfering with carbohydrate digestion and delaying gastrointestinal absorption of glucose. The major side effects are gas, bloating, and diarrhea. Thiazolidinediones are

represented by troglitazone, rosiglitazone and pioglitazone. These expensive oral agents work by improving insulin sensitivity in muscle and, to a much lesser extent, in the liver. These drugs decrease plasma triglyceride levels, but such decrease may be associated with weight gain and an increase in LDL-cholesterol levels.

Liver toxicity is a concern requiring monthly monitoring of liver function. Since troglitazone (Rezulinâ) is more toxic to the liver than rosiglitazone and pioglitazone (having resulted in dozens of deaths from liver failure), in March 2000 the FDA asked the manufacturer of Rezulin to remove the product from the market. Meglitinides (drug name Repaglinide) augment insulin secretion, but weight gain, gastrointestinal disturbances, and hypoglycemia are possible side effects.

Insulin Therapy:

Insulin is usually added to an oral agent when glycemic control is suboptimal at maximal doses of oral medications. Some diabet-ologists prefer to initiate insulin therapy in patients with newly diagnosed type 2 diabetes[10]. Weight gain and hypoglycemia are common side effects of insulin therapy [13,16].Vigorous insulin treatment may also carry an increased risk of atherogenesis[14].

Exercise

Any exercise prescription should be individualized to account for patient interests, physical status, capacity, and motivation. Exercising five or six times per week enhances weight reduction. Because many people with diabetes have not been active, exercise should start at a low level and gradually increase to avoid adverse effects such as injury, hypoglycemia, or cardiac problems[17, 18].

Conventional Approach to Diet Therapy

Given the heterogeneous nature of type 2 diabetes, no single dietary approach is appropriate for all patients. Meal plans and diet modifications are generally individualized by a registered dietitian to meet patient needs and lifestyle. A typical conventional approach would recommend a diet composed of 60-65 percent carbohydrate, 25-35 percent fat, and 10-20 percent protein, with limited or no alcohol consumption[19].

The Medical approach of Plants

The world health organization has recommended medical plant research was no attention. Plants have been the major source of drugs in Indian system of medicine and other ancient system in world [17.] Earliest description of curative properties of medical plants was found in Rig Vada (2500-1800 Bc.). Samthita and sushrata a various medicals herbs.

Information on medical plants in India has been systematically organized[18]. In our ongoing search for a therapeutic approach to the treatment of diabetes, we screened extracts from traditional medical herbs for antioxidant and cell-protective effects and used as medicines for the treatment of inflammation related disease and recent studies have reported that their extracts possess antioxidants. Anti-inflammatory and anti-tumor effect[9]. Herbs contain large numbers of active compound such as phenolic acid, flavonoids, and titer period sponins, which have known ROS scavenging effect[10,11]. There are many anti-diabetic plants, which might provide useful source for the development of drugs in the treatment plants with hypoglycemic activity is vast. As many of these plants were used for many centuries and some time as regular constituents of the diet. It is assumed that they do not have many side effects[14]. However chronic consumption of large amounts of traditional remedies must always be taken with caution, as toxicity studies have not been conducted for most of plants[15].

Sulphonylureas and few biguanides are drugs used in the treatment of hyperglycemia in non-insulin dependent diabetes mellitus (NIDDM) but they are unable to lower glucose concentration within normal range and resistant a normal pattern of glucose homeostasis permanently but their pharmacokinetic properties secondary failure rate and side effects [16]. Even insulin therapy does not reinstate a permanently normal pattern of glucose homeostasis and carries an increased risk of atherogenesis and hypoglycemia. Medical plants have the advantage of having little or no side effect. Some of them are being used in traditional system of medicine from hundred years in many countries of the world. Till today metformin is the only ethical drug approved for the treatment of NIDDM patients. This is derived from a medicinal plant Galega officialis and historically used for treatment of diabetes[19].

Ayurvedic herbs for the management of diabetes

Before the advent of insulin injection and other pharmaceutical preparations, healers relied heavily upon herbs to treat diabetes. Although numerous herbs are reported (Table 1) to possess some degree of antdiabetic activity[14], a significant amount of research, as well as traditional usage, suggests that Gurmar leaf (*Gymmnema Sylvetris*), Neem *(Azadiracta indica)*, Jamun (*Eugenia jambolana*), Tulsi (*Ocimum sanctum*), Stevia (*Sweeten*), Kalmagh (*Swertia chirayita* karst), Methi (*Trigonella foenum-graeccum*) may be among the best in terms of efficacy and safety. These, as well as several other valuable herbs such as garlic acid ginseng represent safe, useful adjuncts to conventional therapeutic approaches to diabetes management[25]. Also, it is possible that the insulin and glucose normalizing effect of some of these herbs may benefit the non-diabetic with insulin resistance. An Ayurvedic principal is being exhaustively researched for its effect on blood sugar levels and also it's potential in adverting long-term complications of diabetes mellitus. Its main ingredients are plants extract [26].

Table 1: Herbs and their part used in diabetic medicines

Name of the Ingredients	**Quantity**	**Latin Name**	**Parts Used**
Gurmar		*Gymmnema Sylvetris*	Leaf Powder
Neem		*Azadiracta indica*	Leaf Powder
Jamun		*Eugenia jambolana*	Seed Powder
Tulsi		*Ocimum sanctum*	Leaf Powder
Stevia		*Sweeten*	Leaf Powder
Kalmagh		*Swertia chirayita* karst	Leaf Powder
Karela		*Momardica charanctla*	Fruit Powder
Giloy		*Tinospora cordifolia*	Stem Powder
Khair		*Accacia catechu*	Powder
Haldi		*Curcuma longa*	Rhizome powder
Amla		*Phyllanthus emblica*	Fruit Powder
Vljaysar		*Pterocarpus marsupium*	Wood Powder
Tejpatta		*Cinnamomum tamala*	Leaf Powder
Gular		*Ficus glomirata*	Leaf Powder
Kutki		*Pichorrhiza krurra*	Wood Powder
Methi		*Trigonella foenum-graeccum*	Seed Powder
Vica Russia			Leaf Powder
Purified Shliajeet			Rock Derivative
Powderang Bhasma			Powder
Yasad Bhasma			Powder

Traditional Tonic Plants

***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[27]. 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 (*Gymnema sylvestre*), a standardized extract obtained from *Gymnema sylvestre* leaves [28]. This led to the hypothesis that *Gymnema* extracts could induce the pancreas to secrete insulin, a finding confirmed by later laboratory experiments and clinical studies on Type I and Type II diabetes patients[29].

***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[30]. 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[31]. In view of these effects, *Momordica charantia* is a potential herbal alternative in diabetes management, particularly in non-insulin dependent diabetes [32].

***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. Saponins present in fenugreek seeds have also been shown to lower cholesterol levels in human subjects[33]. Recent studies have revealed the efficacy of defatted fenugreek seed extracts in the management of both Type I and Type II diabetes. 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[34, 35].

***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[36].

***Azadiracta indica* (Neem)**

Neem is one of the most powerful blood purifiers and detoxifiers from India. Neem reduces fever and toxins involved in most inflammatory skin diseases and ulcerated mucous membranes. Neem is used widely for malaria and other intermittent and periodic fevers in India. Neems astringent action promotes healing. Not recommended in cases of severe fatigue or emaciation[37]. Neem is also used in India for skin diseases, parasites, thirst, nausea, diabetes, tumors, obesity, arthritis, rheumatism and jaundice. This information is from Ayurvedic Alternative Medicine Text for your education[38.]

Neem leaf is a traditional herb for treating diabetes and has been scientifically proven effective in treating and preventing diabetes. Oral doses of Neem leaf extracts significantly reduced insulin requirements for non-insulin dependent diabetes. Neem oil has also proven effective and has been able to inhibit increases in blood sugar levels by as much as 45% in test animals. The Indian government has approved the sale by pharmaceutical companies of Neem tablets for diabetics (Some of these preparations are really nothing more than powdered Neem leaves) [39, 40].

***Sweeten* (Stevia)**

If you fall into the category of a consumer who is searching for an excellent natural sweetening agent which is safe, powerful, and calorie-free, stevia extracts should be first on your list. Ironically, while enormous quantities of aspartame and saccharine continue to be consumed in this country, a sweetening substance that poses less risk and is more effective continues to be rigorously regulated. Fortunately, restrictions are easing and it is now possible to purchase stevia as a supplement. Both xylitol and saccharine have been linked to tumor development and aspartame continues to prompt controversy in its reported wide range of negative side effects, yet all of these products enjoy unrestricted marketability. [41] It is rather ironic that chemical compounds that have the capability of wreaking all kinds of havoc with human physiology have the advantage over natural substances that are certainly much more benign. It's hard to imagine that a safe, natural herb which offers concentrated sweetening power and may also actually normalize blood sugar and prevent tooth decay remains relatively unknown[42].

Stevia will inevitably emerge as one of the best non-caloric sweeteners available. It's just a matter of time before American consumers discover its extraordinary attributes. In the meantime, learning to use stevia dietary supplements can provide us with the ability to *"sweeten"* our lives without compromising our health. (NOTE: Linda Bonvie, Bill

Bonvie and Donna Gates discuss various biochemical attributes of the herb's glycosides in a comprehensive and engaging book)[43].

***Swertia chirayita* karst (Kalmegh)**

The crude drug consists of dried of fresh leves or the aerial portions of the plants. Sometimes, the whole plant, including the roots, is used. The drug is sometimes mixed with the genuine *chirata* (*Swertia chirayita* karst.) the drug normally should not contain more than two per cent of foreign organic matter. Neither leaf nor stem extracts of kalmegh administered orally matter *S.c*. or orally changed blood sugar level of normal or diabetic rats. Kalmegh increased biliary flow and liver weight in rat and decreased hexobarbital-induced sleep time. It is less potent than Phenobarbital[44.]

***Eugenia jambolana* (Jamun)**

When alloxan induced diabetic rats were fed with Jamun seed extract, the blood glucose, blood urea, serum cholesterol and serum triglyceride levels were found to decrease significantly [45]. Jamun fruit reduces the sugar in the blood and is very good in the control of diabetes. Its seeds contain Glucoside, Jamboline and Ellagic acid, which are reputed to have the ability to check the conversion of starch into sugar in case of excess production of glucose [44]. Therefore, Jamun seeds are also used as a remedy for Diabetes. "Shaligram Nighantu Pharmacopia" in ancient India also confirmed use of Jamun seeds for Diabetes.Other constituents of the fruit include Resin, albumen, gallic acid, essential oil and tannic acids (http://www.healthandyoga.com/html/ product/diabetic.html)[45]. Tribals use Jamun leaves as such in diabetes needing further studies to show the efficacy of the leaves. 5-6 leaves per day are commonly chewed in morning before the breakfast.

Scientific basis for using mixed formulations

Ayurvedic remedies for diabetes are usually mixed formulations 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 feature predominantly in the progression of the disease and its secondary complications[53, 61]. The inclusion of immunomodulators, and detoxifying antioxidants in mixed formulations is therefore beneficial. Some traditional formulations also contain cholesterolreducing agents and adaptogens such as *Emblica officinalis* [54, 63].

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[55]. 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[56,62,64]. For instance, recent studies

suggest that *Garcinia cambogia* extract efficiently improved glucose metabolism and displayed leptin-like activity in mice. *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* that support weight management may be beneficial if used in combination with conventional drugs such as metformin[57]. Vascular inflammation is now regarded by medical researchers as the key underlying cause for several chronic disease conditions, including diabetes. 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[58]. 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[59]. A comprehensive Ayurvedic therapeutic regimen thus offers time tested safe and effective support to conventional therapy in the management of diabetes[60,66,65]. 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 [61].

In fact diabetes now a day is a global problem because every year a considerable amount of foreign exchange is involved in the import of the drugs of foreign origin. The utilization of indigenous drug resources with importance of the local industry on the one hand and will minimize the expenditure incurred on the purchase of foreign drugs on the other. In view of the economic importance of medicinal indigenous plants, research and development efforts should be focused on these plants. So it is strongly recommended to carryout phytochemical and clinical research work of the indigenous plants to prove and substantiate the traditional phytotherapies of the rural people. The clinically active plants should be studied along with active compounds, which are responsible for the hypoglycemic activities. Compounds from these plants with proven results may then be synthesized in large amount commercially for wider circulation throughout the world for global marketing.

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