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Review Article

HERBAL MANAGEMENT OF DIABETES MELLITUS: A RAPIDLY EXPANDING RESEARCH AVENUE

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ABSTRACT

Conventional drug therapy though effective in the management of diabetes mellitus is expensive and has toxic side effects. Herbal medicine would thus provide alternative therapy if effective and less toxic. This paper reviews the use of various antidiabetic plants in management of diabetes mellitus. Their documented modes of actions along with *in vivo* are also discussed.

Keyword: Herbal medicine, Diabetes mellitus, Antidiabetic plants, Toxic side effects.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by high blood levels of glucose due to absence of insulin or improper utilization of insulin by target cells.[1] It can be associated with serious complications and premature death, but people with diabetes mellitus can take steps to control the disease and lower the risk of complications.[2] Despite having been a rare disease years ago, its incidence has reached an alarming level, attaining a global incidence of 151 million people per year, of these, more than a half of live in Asia (44 million in the Western Pacific Region, 35 million in South East Asia, 17 million in the Eastern Mediterranean and Middle East region), 8.5 million live in Europe, and 2.5 million live in Africa.[3,4]

"Diabetes will be one of the most challenging public health problems of the 21st century," warned Ms de Alva, International Diabetes Foundation (IDF) president.[5] "The situation is particularly worrying in developing countries, where detection is poor and insulin not always available and where the availability of care, access to care and organization of care cause frequent problems. The IDF must focus on the developing world and become an even more effective advocate for people with diabetes in every corner of the world", pointed out IDF President-Elect, Professor Sir George Alberti.[5]

In 1997 the World Health Organization predicted the number of diagnosed cases of DM would rise from 125 million in 1995 to an estimated 300 million in 2025.[3] Over the past century, DM has been considered a rare medical condition in Africa, as illustrated by the famous statement of Dr Cook who wrote "... diabetes is very uncommon but very fatal..."in his 1901 notes on the diseases met in Africa.[6] However, epidemiological studies carried out in the last decade of the 20th century have provided evidence of a different picture. Diabetes prevalence is characterized by a tremendous rise in the burden of noncommunicable diseases.[7,8]

Heredity is a major factor in the development in diabetes mellitus. If both parents have type II diabetes, there is a chance that nearly all of their children will have diabetes. If both parents have type I diabetes, fewer than 20 percent of their children will develop type I diabetes. If one of identical twins develops type II diabetes, chances are that nearly 100 percent the other twin will also develop it. In type I diabetes, however, only 40 to 50 percent of the second twins will develop the disease, indicating that while inheritance is important, environmental factors (for example, food, stress, viral infection, among others) are also involved in the development of type I diabetes.[9]

The major complications of diabetes mellitus are retinopathy, neuropathy, nephropathy, angiopathy, susceptibility to infections, hyperlipidemia, ketoacidosis, and hyperglycaemic hyperosmolar non-ketonic coma. These complications result in increased disability, reduced life expectancy and enormous health cost for virtually every society.[10,11]

The major therapy option in diabetes mellitus is lifestyle management. Besides exercise, weight control and medical nutrition therapy, oral glucose-lowering drugs and insulin injection are the conventional therapies for the disease.[12] These conventional therapies have adverse side effects, are expensive and require expertise.[2]

Role of Medicinal Plants in Management of Diabetes Mellitus

There is a new trend in the world to turn back to natural substances to avoid the side effects associated with synthetic drugs.[13] Many plant species have been used to treat life- threatening diseases including diabetes mellitus. A World Health Organization (WHO) study shows that 80% of the world population solely relies on medicinal plants for their primary health care needs.[14] It is estimated that the numbers of medicinal plants in the world vary between 30,000 and 75,000.[15] Plants are known sources of useful compounds used for making insecticides, fungicides and industrial raw materials.[16] The majority of drugs active against infections are in fact developed from natural products.

Diabetes has been treated with plant medicines since antiquity. Recent scientific investigation has confirmed the efficacy of many antidiabetic plant preparations some of which are very effective and relatively non-toxic.[2] Before the advent of insulin, diabetes was treated with plant medicines. In 1980, the World Health Organization urged researchers to examine whether traditional medicines produced any beneficial clinical results. In the last 10 to 20 years, scientific investigation has confirmed the efficacy of many of these preparations, some of which are remarkably effective.[17] As an alternative approach, medicinal herbs with antihyperglycemic activities are increasingly sought by diabetic patients and health care professionals. Commonly used herbs and other alternative therapies, less likely to have the side effects of conventional approaches for type II diabetes, have been exploited.[18]

To date, over 400 traditional plant treatments for diabetes have been reported. However, only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type II diabetes. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated.[19]

Plant derivatives with purported hypoglycemic properties have been used in folk medicine and traditional healing systems around the world. They have been used by the Native American Indian and Jewish, Chinese, East Indian, Mexican.[20-22]

Oral administration of *Aloe vera* juice reduces fasting glucose and triglyceride levels in patients with type II diabetes mellitus.[23] Preliminary studies suggest that *Aloe vera* juice may help lower blood sugar levels in people with type II (adult onset) diabetes. The herb has proved to be a useful addition to the diet, exercise, and medication program for type II diabetics.[24]

Garlic (*Allium sativum*) has been reported to have lipid lowering, anti-hypertensive, anti-platelet, antioxidant, and fibrinolytic effects. When used with sulphonylureas, garlic may lower blood sugar considerably.[24, 26]

Many modern pharmaceuticals used in conventional medicine have also a natural plant origin. Among them, metformin derived from the flowering plant, *Galega officinalis* (Goat's Rue or French Lilac), is a common traditional remedy for diabetes.[27, 28] *Galega officinalis* is rich in guanidine, the hypoglycemic component.[29-31] Since guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became available. However, experience with guanidine and biguanides prompted the development of metformin.[2,33]

Gymnema sylvestre, a plant native to the tropical forests of India, has long been used as a treatment for diabetes. In a study of type II diabetes, 22 patients given 400 mg/kg body weight of the aqueous leave extracts of *Gymnema sylvestre* daily along with their oral hypoglycemic drugs, showed improved blood sugar control. Twenty-one of the 22 reduced their oral hypoglycemic drug dosage, and five patients discontinued oral medication and maintained blood sugar control with the *Gymnema* extract alone.[34] *Gymnema sylvestre* enhances the production of endogenous insulin there by lowering blood glucose levels.[35,36]

The aqueous leave extracts of *Vaccinium myrtillus* (bilberry or European blueberry) were widely used as a treatment for diabetes before the availability of insulin.[19] Oral administration of bilberry leaf tea reduced blood sugar levels in normal and diabetic dogs, even when glucose was concurrently injected intravenously.[37] Bilberry also has a beneficial effect in microvascular abnormalities of diabetes,[38,39] particularly retinopathy. In the case of vascular complications, however, the fruit is used, with the anthocyanosides being the most important constituent.[40]

Pterocarpus marsupium and other Epicatechin-containing plants have also demonstrated potential to manage diabetes mellitus. *Pterocarpus marsupium* has a long history of use in India as a treatment for diabetes. The flavanoid, (-)-epicatechin, extracted from the bark of this plant prevents β-cell damage in rats. In addition, both epicatechin and a crude ethanol extract of *Pterocarpus marsupium* regenerate functional pancreatic β-cells in diabetic animals.[41,42] Epicatechin and catechin consist of glycosides and esters. They are flavan-3-ols; a group of flavanols that have anti-diabetic properties.[43] *Camellia sinensis* (green tea polyphenols) and *Acacia catechu* (Burma cutch) are also good sources of flavan-3-ols.[18]

Trigonella foenum graecum (fenugreek) is used as a remedy for diabetes, particularly in India.[44] The active principal is in the defatted portion of the seed, which contains the alkaloid trigonelline, nicotinic acid, and coumarin. Administration of the defatted seed (1.5-2.0 g/kg daily) to both normal and diabetic dogs reduces fasting and postprandial blood levels of glucose, glucagon, somatostatin, insulin, total cholesterol, and triglycerides, and increases HDL-cholesterol levels.[45] Human studies have confirmed the glucose- and lipid lowering effects.[46] At least 50 percent of seeds is fiber and constitutes another potential mechanism of fenugreek's beneficial effect in diabetic patients.[47]

The methanolic leave extracts of *Momordica charantia,* also known as bitter melon, balsam pear, or karela, has also been used extensively in folk medicines as a remedy for diabetes. The blood sugar-lowering action of the fresh juice or unripe fruit has been established in animal experimental models as well as human clinical trials.[48, 49]

The aqueous Kenyan plant extracts *Bidens pilosa, Erythrina abyssinica, Aspilia pluriseta, Strychnos henningsii* and *Catha edulis* have been shown to significantly lower blood glucose to normal and as effectively as insulin and at times beyond the lowering effect of insulin in alloxan-induced diabetic mice.[2]

Allium cepa contains hypoglycaemic allylpropyl disulfide (APDS).[25,26] Stevia has been used traditionally to treat diabetes. Early reports suggested that stevia might have beneficial effects on glucose tolerance (and therefore potentially help with diabetes), although not all reports have confirmed this.[22]

Ginkgo biloba extract has proved useful for prevention and treatment of early-stage diabetic neuropathy.[50]

Traditional Chinese herbs are very effective in treating patients with type II diabetes mellitus. When prescribed correctly, Chinese herbs lower blood glucose levels, manage common signs and symptoms, and treat the complications of diabetes mellitus. Patients generally respond to herbal treatment within 3-4 weeks, with significant reduction in blood glucose levels and little fluctuation throughout the day. However, some patients may require up to 6-8 weeks. For patients with type I diabetes mellitus, Chinese herbs are used in conjunction with insulin to manage symptoms and complications. Chinese herbs can also reduce the frequency and dosage of insulin injections.[1]

Asian ginseng is commonly used in traditional Chinese medicine to treat diabetes. It has been shown to enhance the release of insulin from the pancreas and to increase the number of insulin receptors. It also has a direct blood sugar-lowering effect. A recent study found that 200 mg of ginseng extract per day improved blood sugar control as well as energy levels in type II diabetes (NIDDM).[50] These agents are cheap, readily available and have limited side effects.

Ether and Ethyl acetate extracts of the leaf of *Sarcococca saligna* showed significant reduction in blood Glucose level in 18h fasted rat model compared to 0h blood glucose level and in High Fatty Diet Fed, Streptozotocin treated Rats compared to High Fatty Diet, Streptozotocin control.[51]

In a study to evaluate the antidiabetic effect of *Melia azadirach* and its histological parameters in Alloxan induced diabetic albino rats, it was observed that oral administration of chloroform extracts of Melia leaf (250 and 500mg/kg body weight) for 30 days resulted in significant decrease of blood glucose from 298.62±22.32 to 80.52 ± 04.71 and decrease in the activities of enzymes of liver. The results showed not only significant anti-hyperglycemic effect of Melia extracts in experimental model of diabetes mellitus but also indicated a dose dependant activity of the extracts.[52] Histological studies of *Melia azadirach* in Alloxan induced albino rats, sampling and staining of pancreas, spleen, liver and kidney tissues of diabetic and normal rats showed strong antigenesity in beta-cells of the islets in control. Majority of the cells were apparently protected from light degeneration when treated with 25 and 50 ml/kg/bw of Melia and moderate antigenesity was noted in beta-cells of the islets of langerhans of the pancreatic tissue.[52]

A research was performed to characterize the hypoglycemic effect of ethanolic leaf extract of *Dalbergia sissoo* L. leaves in alloxanized diabetic rats had findings indicating the hypoglycemic and potential antihyperglycemic nature of the extract. It was also found to be 12% more effective in reducing the blood glucose level compared to the standard drug Glibenclamide.[53]

In a study to investigate the effect of the orally administered aqueous extract of *Carissa carandas* on alloxan induced and normoglycemic Wister rats, the results showed that at the dose of 250 mg/kg body weight, the extract did not show any significant change in the blood glucose levels when compared to untreated control. Further, the doses of 500 and 1000 mg/kg body weight of extract showed a significant decrease in blood glucose levels after 4, 8 and 24 hours. In normoglycemic rats, the dose of 1000 mg/kg body weight of the extract significantly decreased the blood glucose levels at 8 and 24 hours. The study concluded that the doses of extract had shown both significant hypoglycemic and antihyperglycemic effects in Wister rats.[54]

A study aimed at investigation of antioxidant, antidiabetic and antihyperlipidemic potential of methanolic and aqueous extracts of

Luffa acutangula fruits revealed that the methanolic extract at a dose of 100 mg/kg body weight was found to be active but the antidiabetic activity was increased significantly at a dose of 200 and 400 mg/kg body weight as compared to the aqueous extract. Besides, the methanolic extract had dose dependent pronounced antihyperlipidemic activity over the aqueous extract. The study concluded that both the methanolic and aqueous extracts of *Luffa acutangula* had antidiabetic and antihyperlipidemic activity although the methanolic extract was superior to the aqueous extract in management of diabetes and its associated lipid imbalance.[55]

A study to investigate the effects of crude Dichloromethane, Ethyl Acetate and Butanol extracts of *Coscinium fenestratum* on streptozotocin-induced diabetic rat's models showed that the plant has significant antidiabetic potential.[56] The crude stem extracts at concentration of 250mg/kg body weight were administered for 4 weeks and the effects of extracts on blood glucose, body weight and carbohydrate metabolizing enzymes Hexokinase and Lactate Dehydrogenase were determined as well as determination of the total phenolic content, anti-oxidant activity and phytochemical screening and HPLC profiling of extracts. Dichloromethane and Ethyl acetate extracts were found to habour a significant hypoglycemic effect by lowering the blood glucose levels and increasing the body weight in Streptozotocin induced diabetic rats. The activities of hexokinase and Lactate Dehydrogenase increase in the diabetic group treated with Dichloromethane and Ethyl acetate extract compared to the diabetic rats group.[56]

The total phenolic content and antioxidant studies revealed the presence of phenolic and antioxidant activity in Dichloromethane and Ethyl acetate extracts. Phytochemical screening, total phenolic content of Dichloromethane and Ethyl acetate extracts confirmed the presences of phenols, alkaloids, flavonoids, terpenes, saponins, tannins, steroids and possess strong antioxidant properties. The study concluded that Dichloromethane and Ethyl acetate stem extracts *Coscinium fenestratum* showed strong plasma glucose lowering and antioxidant activity. These effects were attributed to the presence of alkaloids, flavonoids, terpenes, tannins, and steroids in Dichloromethane and Ethyl acetate stem extracts.[56]

Medicinal plants have also been used to manage diabetes complications. In a study to analyze the hypolipidemic effects of methanol extract of *Costus igneus* leaves in streptozotocin-induced diabetic rats, male diabetic rats were treated with 100 mg/kg/day of methanolic extract orally for 30 days. The experiment showed promising results by significantly decreasing cholesterol, triglycerides, free fatty acids and phospholipids in the liver, heart and kidney of diabetic treated rats. Lipoproteins restored normal levels in treated group, significantly reducing serum total cholesterol and increasing High Density Lipoproteins (HDL)-cholesterol. Activity of lipoprotein lipase was enhanced in extract treated group. Glucose-6-phosphate dehydrogenase, LCAT and malic enzyme activities which were significantly lower in diabetic rats showed considerable increase in treated rats. The study, therefore, indicated that methanolic leaf extract of *Costus igneus* exerts potent hypolipidemic effects in diabetic rats. Hence the plant may also be useful in the cure and management of secondary complications of diabetes.[57]

The leaf extracts of *Albizzia lebbeck* (Benth), *Psidium guajava* (Linn), and *Trigonella foenum-graecum* (Linn), were tested for their antihyperglycaemic and antidiabetic potential on alloxan and streptozotocin induced diabetic models of mice. All leaf extracts tested showed a positive trend in regulating blood glucose levels in Swiss albino mice. Rosiglitazone was taken as a standard drug.[58]

The anti-diabetic efficacy of bitter leaf (*Vernonia amygdalina*) leaf meal (VALM) was evaluated using broiler finishers'. Using 0%, 5%, 10% and 15% VALM representing diets A,B,C,D respectively to replace groundnut cake (GNC) in broiler finishers' feed, a total of 144 Marshal brooded broilers weighing 500 – 610g were used in a study that lasted for 28 days. At the expiration of the experiment, 3 birds per treatment were randomly selected and bled for blood samples. The biochemical indices determined included Glucose, Urea, Creatinine, Total protein and Globulin. The results indicated that the use of *V. amygdalina* did not significantly affect the serum urea and creatinine of broiler birds. However, there was a significant decrease in blood glucose of the chicken as the level of inclusion of VALM increases.[59]

In addition, significant differences were observed in total protein and globulin of the birds. The percentage reduction of glucose was 14.30%, 22.90% and 28.60% for treatments B, C and D respectively. These results clearly indicate that the administration of *V. amygdalina* at varying levels produced hypoglycaemic effects. Besides, *V. amaygdalina* did not seem to have adverse effect on the liver and kidney, since the serum urea and creatinine levels were not significantly altered. It could be inferred that *V. amaygdalina* besides exhibiting hypoglycaemic activity is also safe for consumption as food or medicine, since there were no indication of toxicity judging from the values of the biomolecules evaluated.[59]

A preliminary study was undertaken to evaluate the antidiabetic effect of the aqueous root extract by oral glucose tolerance test (OGTT), normoglycaemic and antihyperglycaemic activity in streptozotocin (STZ)-nicotinamide induced non insulin-dependent diabetes mellitus rats. Graded doses (250 and 500mg/kg) of the aqueous root extract suspended in gum acacia were administered to normal and experimental diabetic rats. Effect on glucose tolerance test showed a significant fall in the blood glucose level of extract treated animals after 1 hr, indicating its hypoglyaemic activity. Continuous blood glucose lowering activity was observed till 4 hr of administration in normoglycaemic and diabetic rats. The results were compared with standard drug glibenclamide.[60]

CONCLUSION

It is clearly evident that herbs have immense potential to provide bioactive compounds that can be developed into antidiabetic agents. Despite this potential, antidiabetic plants remain grossly understudied and under-utilized as a source of novel drugs, especially in the developed countries. The reviewed literature indicates that there is untapped potential in medicinal plants for management of diabetes mellitus. Therefore this review seeks to serve invoke more interest in bioscreening of as many medicinal plants as possible for their hypoglycemic potential. Such efforts will aid development of novel plant-derived antihyperglycemic agents. However, more detailed research on the the safety of these antidiabetic plants needs to be undertaken to eradicate all the concerns, if any, on their efficacy to manage diabetes mellitus.

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