THE ROLE OF MEDICINAL PLANTS IN THE TREATMENT OF TYPE-2 DIABETES

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ABSTRACT
Diabetes mellitus is a hampering and often life-threatening ailment. It has an increasingly frequency of occurrence throughout the world. Concomitantly, a scientific investigation of traditional herbal remedies for diabetes may provide an exciting opportunity for discovering new leads in order to develop alternative drugs and therapeutic strategies particularly in the third-world countries. This review provides information on several species of plants reported to have been used to treat diabetes and/or investigated for antidiabetic activity. It also highlights how these natural alternatives overweight the medicines available today in the market. Many traditional plant treatment have been recorded, but only a small number of these have received scientific and medical evaluation to assess their efficacy. Therefore, a big chance for further investigations and isolation of biologically active compound is present.

Keywords: Diabetes mellitus; Medicinal plants; Antidiabetic; Hypoglycemic

INTRODUCTION
Diabetes continues to be on the of the world’s persecuting epidemics. It is a metabolic disorder involving multifactorial aspects with a heterogeneous nature as it involves disturbances in the lipids and carbohydrates metabolism. The word diabetes is originally derived from the ancient Greek “Diabetes”, which literally means “a passer through” an indication to the excessive excretion of urine or polyuria, a dominant characteristic of the disease.

Diabetes diagnosis and treatment methods were known since antiquity. Several historical records reveal that the disease was quite known among early physicians and that herbal medicine has been used for several thousand years to manage diabetes.

Inspire of the great improvements humanity has done in the past century to effectively to control and manage this disease, there is no ultimate cure until the present day. If not managed properly, long term elevated blood glucose levels can result in a series of distressful complications. These, in turn can be broadly categorized in to Macro- and microvascular complications.
The macrovascular complications include: stroke, foot problems, peripheral vascular diseases, heart problems and hypertension, whereas, the microvascular ones include various retinopathies, nephropathies and neuropathies.

These complications still bother the patients and the healthcare providers as well. According to recent statistics, the number of diabetic patients will rise by 150% in the next 20 years, with an increasing percentage of the younger age groups. It is estimated that the number of diabetic patients will be 366 million in 2030 which will represent a huge financial burden on the patient’s families as well as the governments’ healthcare systems.

**Diabetes Mellitus in Saudi Arabia**

While the prevalence of diabetes mellitus in the world varies drastically, it mainly takes place in the adult population of the developed countries. Saudi Arabia is one of top ten countries in the world in number of DM patients. The list also includes China, Russia and the United States. The percentage of DM patients in Saudi Arabia is around 27% of the total population. Most of Diabetes Mellitus patients in Saudi Arabia are women living in cities and the main cause is obesity.

**Goals of Management in Diabetes Mellitus**

Management of Type 2 Diabetes aims at achieving different goals, one of which is to reduce the symptoms of hyperglycemia which usually hinders the patient’s everyday life including polyphagia, polydipsia and polyuria. Another goal is to demote the onset and progression of long term complications. Intensive therapy is also incorporated to decrease the associated cardiovascular risk factors and ultimately improve life quality and expectancy. As mentioned before, until now there is no final cure from DM but management remains the ultimate resort to prevent or delay the complications as the group of genes responsible for the disease is not well understood.

**Current Orthodox Medications**

The current diabetes medications available are insulin and oral hypoglycemic agents (Sulfonylureas, Biguanides, Alpha-glucosidae inhibitors, Thiazolidinediones and Meglitinides). The success of oral antidiabetics is limited by their mechanisms of action, which often addresses the symptoms of diabetes rather than its pathophysiology. Throughout the decades that followed their introduction to the market by large pharmaceutical companies, it was observed from the population safety data that these drugs had common undesirable side effects such as minor hypoglycemia and gastrointestinal problems.

Other common side effects include peripheral edema which is observed in up to 26% of thiazolidinediones treated patients and body weight increase of (1 to 5 kg) is unexceptional with both Sulfonylureas and thiazolidinediones therapy.

**Inadequacies of Current Antidiabetic Treatments**
Antidiabetic Agent | Limitations
--- | ---
Insulin | Weight gain, Hypoglycemia
Thiazolidinediones | High cost, liver toxicity, high LDL cholesterol, weight gain
Sulfonylureas | Weight gain, Hypoglycemia
Alpha - glucosidase inhibitors | Gastrointestinal disorders
Biguanides | Gastrointestinal disorders
Meglitinides | Weight gain, hypoglycemia

Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently takes place with the disease\textsuperscript{vi}. Another problem with these agents was detected: according to literature, two-thirds of the medications prescribed for diabetic children have not been proven to be safe or effective for this important patient population\textsuperscript{vii}. The limitations of currently available oral anti-diabetic agents either in terms of efficacy and safety coupled with the emergence of the disease into a global epidemic have encouraged a concerted effort to discover drugs that can manage type 2 diabetes more efficiently.

**Alternative Approaches**

Alternative treatments derived from natural sources for diabetes have become increasingly popular the last several years including nutritional supplementation, acupuncture and medicinal herbs. As the disease is becoming progressing undiminished, the (WHO) Expert Committee on diabetes has recommended the ethnobotanical herbs should be further investigated. Phytoconstituents with anti-diabetic activity derived from herbs used even in prehistoric eras are now researched extensively and revealed using today’s modern sophisticated technology, particularly in India.\textsuperscript{viii} Ethno-pharmacological surveys indicate that about 1200 plants were used in traditional medicine for their alleged hypoglycemic activity, although only a small number of these have received scientific and medical evaluation to assess their efficacy.\textsuperscript{ix}

**The Story of Medicinal Plants and Diabetes**

Physicians since early times, especially in ancient India listed specific managements for diabetes, including dietary modifications, medicinal plants and minerals.\textsuperscript{viii} For example, Raw onion bulbs (\textit{Allium cepa}) and garlic cloves (\textit{Allium sativum}) have long been used as dietary supplements for the traditional treatment of diabetes in Asia, Europe, and the Middle East.\textsuperscript{viii} In 1929, Glazer and Halpern reported the first evidence that natural products (yeast) have insulin-potentiating property. In 1979, Bever and Zahid published a list of plants which had oral hypoglycemic action.\textsuperscript{xii} In 1986, Saudin, a novel terpenoid substance which showed hypoglycemic properties, was isolated from the plant \textit{Cluytiarichardiana}.\textsuperscript{xiii} In 1988, it was discovered that certain spices like cinnamon and turmeric displayed insulin potentiating activity. The plant families, including the species, most studied for their confirmed hypoglycaemic effects include:
Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae. The most studied species are: Citrullus colocynthis (Cactaceae), Trigonella foenumgraecum (Leguminosea), Momordica charantia (Cucurbitaceae), Ficus bengalensis (Moraceae), Polygala senega (Polygalaceae) and Gymnema sylvestre (Asclepiadaceae). xiv

Examples of Clinical Trials on Plants as Antidiabetics

Ginseng Species
Several studies have clinically confirmed the hypoglycemic activity of Ginseng. Sotaniemi et al demonstrated a reduction in the levels of fasting blood glucose in type 2 diabetics treated with a small dose (100-200 mg) of ginseng relative to placebo xv. Vuksan et al also demonstrated that 3g American ginseng, when given 40 minutes prior to the test meal, significantly lowered the blood glucose in both non-diabetic subjects and type 2 diabetic patients. xvi As the possibility of hormone-like or hormone-inducing effects cannot be ruled out, some researchers suggest limiting treatment to three months. xvii

Momordica charantia (Bitter Melon)
Bitter melon is composed of several compounds with confirmed anti-diabetic properties. Alcohol-extracted charantin from Momordica charantia consists of mixed steroids and it was confirmed to be more potent than the oral hypoglycemic agent tolbutamide in an animal study. Bitter melon also contains a bovine insulin-like polypeptide, polypeptide-P, which is also known as the vegetarian polypeptide (polypeptide-V). This polypeptide was established in an interesting study performed in India to decrease blood sugar levels when injected subcutaneously into type 1 diabetic patients. xviii The oral administration of bitter melon preparations has also shown satisfactory results in clinical trials in type 2 diabetic patients. Dosages of capsulated dried powder range from 3-15g daily. That is quite a large dose so to avoid the necessity of taking so many capsules; a standardized extract may be used at dosages of 100-200 mg three times daily.

Fenugreek
Human studies have confirmed the glucose and lipid-lowering effects of Trigonella foenum graecum. In type 2 diabetic patients, the ingestion of 15 g of powdered fenugreek seed soaked in water significantly reduced the postprandial glucose levels during the glucose tolerance test, because of the possibility of affecting the blood sugar by slowing absorption, oral medications should be taken at a different time than fenugreek. xix

Gurmar
On the US market several years ago as a “sugar blocker”. In a study of type 2 diabetes, 22 patients were given 400 mg the extract daily along with their oral hypoglycemic drugs. All patients
demonstrated improved blood sugar control. Twenty-one of 22 were able to reduce their oral hypoglycemic drug dosage considerably, and five patients were able to discontinue oral medication and maintain blood sugar control with the extract alone. There is no decisive mechanism of Gurmar’s pharmacological action but it was postulated that Gymnema sylvestre enhances the production of endogenous insulin.\textsuperscript{xx}

The NAPRALERT database lists large numbers of plants’ species representing 725 genera in 183 families extending from the marine algae and fungi with anti-diabetic activity.\textsuperscript{xxi} Some herbs have been proven to help in the regeneration of β-cells and in overcoming resistance.\textsuperscript{xxii} In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol-lowering action.\textsuperscript{xxiii}

Possible Advantages of Medicinal Plants over Existing Drugs

The wide range of plant constituents could have different sites of action within the body. Although an orally active botanical substitute for insulin seems unlikely in the foreseeable future, new molecules to stimulate endogenous insulin biosynthesis and secretion (and to promote insulin action) are realistic possibilities. Traditional anti-diabetic plants might provide a useful source of new oral hypoglycemic compounds for future development as new pharmaceutical entities, or as simple dietary adjuncts to existing therapies as the multifactorial pathogenicity of diabetes demands multi-modal therapeutic approach. Therefore, future therapeutic strategies require the combination of various types of multiple agents. Poly-herbal formulations have the synergistic, potentiative, agonistic/antagonistic pharmacological agents within themselves due to incorporation of plant medicines with diverse pharmacological actions. These pharmacological principles work together in a dynamic way to produce maximum therapeutic efficacy with minimum side effects.

Possible Limitations of Medicinal Plants Use

Unfortunately, despite the apparent supremacy in terms of multiple therapeutic approaches of herbal medicines, well-organized, rigorous clinical trial evidences are not adequately available in order to advocate their scientific merit and supremacy over the existing drugs. Though the markets for herbal medicines are booming and evidence for effectiveness is growing, it is also being simultaneously counterbalanced by inadequate regulation. Therefore, proper standardization, efficacy, safety and therapeutic risks/benefits associated with the use of herbal medicines need accurate evaluation.\textsuperscript{xxiv} A rigorous clinical investigation to confirm and advocate the excellence over the existing therapies of traditional medicinal plants, preparation(s), mechanism(s) of action and therapeutic effects is absolutely required.

Recent Successes of Plants

Many ethno-botanical surveys on medicinal plants used by the local population shave been done in different parts of the world.
and there is a considerable number of plants described as anti-diabetic. In addition, a variety of compounds have been isolated, (alkaloids, glycosides, terpenes, flavonoids etc.) but further studies need to be done so as these ‘leads’ could be developed into clinically useful medicines. For example the famous product metformin which is a derivative natural product, galegine, isolated from the plant Galega officinalis.\textsuperscript{xxv}

Another example is the monosaccharide miglitol (developed by Bayer). It is a $\alpha$-glucosidase inhibitor which was synthesized starting from the naturally occurring 1-deoxynojirimycin as a lead structure. Interestingly, 1-deoxynojirimycin can be isolated from both culture broths of streptomycetes and the bark of mulberry trees.\textsuperscript{xxvi}

Another interesting discovery was nordihydroguaiaretic acid (ndga) from plant Larrea tridentata which besides being active orally in diabetic mice also lowered cholesterol levels. This is considered as the unique quality of herbs, which was not observed in any synthetic medicines.\textsuperscript{xxvii}

Nordihydroguaiaretic Acid

Numerous medicinal preparations in various forms have been tested and are used in the Ayurvedic system of medicines for diabetes. These preparations may contain the aqueous extracts or powders of the different parts of the plants that are used in the treatment of diabetes. Examples of these
include; Hyponidd tablets: *Momordica charantia, Swertia chirata, Melia azadiracta, Tinospora cordifolia, Gymnema sylvestre, Enicostemma litterole, Emblica officinalis, Eugenia jambolana, Cassia auriculata & Curcuma longa.*

CONCLUSION

Medicinal plants were used for the management of Diabetes Mellitus for centuries. Even though a botanical substitute for insulin seems unlikely, traditional treatments may provide valuable clues for the development of new oral hypoglycemic agents and simple dietary adjuncts. Another fact worth mentioning is the role of medicinal plants in the chronic diseases management is better than their role in that of the acute ones.

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