THE SEARCH FOR PLANTS TO MANAGE DIABETES

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Contents

Summary
This chapter describes the methods, process and history of the search for plants to manage type 2 diabetes. Ethnomedical and ethnobotanical field research methods are provided to facilitate the search for plants that can manage type 2 diabetes. A brief description of the most commonly reported bioactive compounds is presented along with information on in vivo animal models that are frequently utilized to test for glucose lowering activity in plants utilized in traditional medicine. Several of the most well documented plant species utilized to treat type 2 diabetes are briefly described.

1. Introduction

Healers and physicians have been treating people with diabetes for millennia. There are descriptions of clinical conditions resembling diabetes in the *Ebers Papyrus*, written in roughly 500 B.C. In the Classical Brahmanic period (700-200 B.C.) in India, medical

doctors diagnosed diabetes by tasting the patients urine for sweetness, as well as other symptoms. One Ayurvedic textbook, the *Sushruta Samhita* written in the fourth century B.C., describes two types of diabetes, indicating that 2500 years ago Ayurvedic physicians recognized and distinguished between insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus (NIDDM). Classival symptoms of NIDDM are as follows:

- Polyuria: increased volume of urine (no pain on urination)
- Polydipsea: increased thirst
- Glucosuria: increased sugar in urine
- Fatigue, muscle weakness
- Obesity may or may not be present

The physicians of ancient India listed specific treatments for diabetes, including dietary modifications, medicinal plants and minerals. Chinese medical texts written in 3000 B.C also described diabetes and its treatment. Historical accounts such as these indicate that diabetes was well known among early physicians and that phytomedicines have been used for several thousand years to manage diabetes.

1.1 Diabetes Type 1

The two major types of diabetes mellitus are Type 1 (insulin-dependent diabetes mellitus (IDDM), also called juvenile onset diabetes) and Type 2 (non-insulin dependent diabetes mellitus/NIDDM). Although sometimes known as “adult onset diabetes”, Type 2 Diabetes is now occurring with an alarming frequency in the pediatric populations of developed countries. Type I diabetes evolves from the collapse of pancreatic insulin production. It can only be treated with daily injections of manufactured insulin, and rigorous diet control to balance glucose levels. It is extremely unlikely that novel plant treatments will be discovered to treat this type of diabetes. Type 2 diabetes is a different situation altogether. Its causes are multifactorial and there are no absolute physiologic failures that lead to its development. There are currently a variety of oral medications used to treat it and significant potential for others derived from plant sources. This paper will focus on plant treatments for Type 2 diabetes.

1.2 Diabetes Type 2

Type 2 diabetes is a chronic disease in which the body does not produce enough insulin and/or is resistant to its normal physiologic action. Insulin, a hormone produced by the pancreas acts as a “gate opener” on the cellular level, allowing the cell’s primary energy source, glucose, to pass through the cell membrane and be utilized to power hundreds of essential metabolic processes. When insulin is in low concentrations in the blood compared to the glucose load, high circulating levels of glucose result. Likewise if the insulin “gate opener” mechanism in the cell membrane is “rusty”, abnormally high concentrations of insulin are required to force them open which may be beyond the ability of the pancreas to produce. The result is the same, high blood glucose levels. Over a period of years, high blood glucose levels can lead to complications, including cardiovascular and peripheral vascular disease, suseptability to various infections, diabetic retinopathy (a major cause of blindness), kidney disease, destruction of major joints, and neuropathy (nerve damage). Most of these complications are irreversible,

extremely debilitating and very expensive to care for. Their onset and progression can only be delayed by optimal control of blood glucose levels.

Type 2 diabetes prevalence increases with age, with about 50% of all cases occurring in adults 55 years of age or older. The recent increase in prevalence has been attributed to an increasingly aging population and decreasing mortality from cardiovascular disease. The International Diabetes Federation and the World Health Organization estimate that, world-wide, over 100 million people suffer from Type 2 diabetes and 50% of those cases are undiagnosed. In USA and perhaps other developed nations, there is now a growing subset of pediatric Type 2 diabetics which appears to spring from increasingly sedentary lifestyles, genetic predisposition of some racial groups, and widespread obesity in childhood. The sequelae are the same only the physiologic endpoint may be reached much earlier and would thereafter require even greater use of medical resources over the many remaining years of life.

With no cure for Type 2 diabetes currently available, the disease is managed through medicinal intervention and/or lifestyle modifications. The current treatments available are found within a few general catagories of therapeutic action. Although widely used with a good deal of success, these various medications do not address the needs of all diabetic patients. No one drug or class of drugs is adequate. Many patients start on one class, but often require others and/or combinations. Not infrequently, all oral medictions fail, forcing the patient to switch over to insulin with all it's attendant complexity.

Four main classes of antidiabetic compounds are available to individuals with Type 2 diabetes—sulfonylureas, biguanides, disaccharidase inhibitors, and thiazoldinediones. Sulfonylureas decrease fasting and postprandial glucose levels in Type 2 diabetes patients, primarily by boosting pancreatic insulin secretion. Biguanides (specifically metformin) help enhance the "gate mechanism" making it easier for insulin to do its job. Elevated plasma glucose concentrations improve without increasing insulin secretion. Disaccharidase inhibitors (e.g. acarbose) inhibit the breakdown of disaccharides in the upper gastrointestinal (GI) tract. This inhibition reduces glucose absorbtion as food is digested. Thiazoldinediones are siimlar to biguanides in that they enhance insulin-mediated glucose absorption into cells without raising blood insulin levels.

Patients may not respond or lose responsiveness to a particular therapy. Adverse reactions, such as gastrointestinal intolerance, liver toxicity, or true allergies may occur in otherwise healthy individuals. There may also be unavoidable and unwanted alterations in body metabolism such as hyperinsulinemia (abnormally high insulin levels that may actually damage the cardiovascular system) as with the sulfonylureas. One must also confront the risk of hypoglycemia (abnormally low blood glucose levels that can lead to loss of conciousness or even brain damage), particularly in the elderly. Add to these the inevitability of occasional cross reactions with other medications being used to treat conditions other than diabetes or even other coexisting diseases such as Hepatitis C which weakens the liver and limits the use of any of the potentially hepatotoxic diabetic medications. Finally, patients may simply develop resistance to the actions of a particular medication rendering it useless. It is clear then that alternate therapeutics for Type 2 diabetes are greatly needed as indicated by any of the above scenarios.

First line therapy for Type 2 diabetes is a strictly-controlled regimen of dietary modification, regular exercise and blood glucose monitoring. Of Type 2 diabetes patients, 30% can manage their disease by diet and exercise. When diet and exercise fail, oral medications are prescribed to control persistent hyperglycemia. The degree to which individual patients improve their glucose control is highly variable and dependent on innumerable social, economic, psychological, genetic, and physiologic factors. Existing hypoglycemic therapies are generally ineffective in about 20% of Type 2 cases, due to non-compliance with diet and impaired pancreatic function. Each year on therapy, these drugs become increasingly ineffective in 5% to 10% of treated patients and, over ten years, they remain effective in only 50% of those patients initially responsive.

Culturally appropriate alternative therapies are also desperately needed to treat indigenous populations who are ideologically resistant or otherwise have limited access to western medicine. By searching for plants that manage Type 2 diabetes, researchers and public health officials can document vanishing medical knowledge on potentially effective treatments for this global epidemic.

2. Need for Medicinal Plant Discovery for Type 2 Diabetes

It is projected that the world diabetic population will double by the year 2010 (to 239.3 million people). Type 2 Diabetes has also exploded among indigenous peoples, probably due to adoption of western diets and lifestyles. Among populations of indigenous peoples in USA, including Native Americans, Polynesian Islanders, and expatriate populations of indigenous peoples, Type 2 diabetes is pandemic. Many of these indigenous peoples resist treatment with western drugs by western doctors but are amenable to treatment with medicinal plants because of cultural analogues in their own traditions. Because of this bleak forecast, research on anti-diabetic plants has been strongly encouraged by the World Health Organization.

The total costs associated with Type 2 diabetes in USA are estimated to exceed $90 billion per year, with Type 2 diabetes listed as the fourth leading cause of disease-related deaths. The true mortality may be higher because Type 2 diabetes is under-reported as a cause of death. More than half of all Type 2-related deaths had major cardiovascular disease listed as the underlying cause. Also, patients with Type 2 diabetes are more likely to be hospitalized, and remain hospitalized for longer periods.

3. Methods for Searching for Type 2 Diabetes Active Plants

Ethnomedical and ethnobotanical investigations conducted around the world have indicated that traditional healers often recognize Type 2 diabetes as a clinical entity treatable with specific botanical remedies. Diagnostic criteria and assumed root causes may vary significantly, but keen observation is always employed. Regardless of exact methodology, once diagnosed, patients may be effectively treated by traditional healers for a variety of symptoms, singly or in combination, associated with Type 2 diabetes. Thus, efficacious therapies administered for the abrogation of known diabetic sequelae such as chronic fatigue, tingling in the hands and feet, excessive thirst and urination, foot sores, and fungal infections of the skin or vaginal mucosa—all of which constitute

some of the primary manifestations of Type 2 diabetes—in theory may have blood-sugar-lowering activity.

Local ethnomedical description of urinary signs of Type 2 diabetes include the following:

- increased number of urinations during day and night.
- disease name may include name of animal e.g. some healers among the Igbo in Nigeria call it "ram's urine disease" because the human's increased volume of urine resembles a ram species that produces large volumes of urine.
- report that urine has a sweet taste.
- local disease name often includes a word equivalent to sweet or sugar in the name e.g. sweet urine disease, sugar urine disease or sugar disease.
- local people often report that insects e.g. ants or flies, go to the urine on the ground.
- local people may report that the urine seeps into the ground more slowly.
- local people may report that there is a white patch on the ground where the urine has dried.

3.1. Ethnomedical search for plants to treat Type 2 diabetes

A starting point for ethnomedically-directed search for plants to treat Type 2 diabetes, is identification of plant species used by traditional healers for this purpose. Traditional cultures around the world have access to hundreds of different plant species in the ecosystems where they live. The total number of plants used as medicines is typically large, but there is usually a relatively small subset of plants selected to treat each specific disease. A very important feature of prioritizing the therapeutic value of Type 2 diabetes medicinal plants is evaluating both quantitative and qualitative features of the ethnomedical information. Studies have shown that taking into account the ethnolinguistic knowledge on plants to guide biological screening results in identifying a high percentage of biologically active plants, as determined using laboratory or animal models of diabetes. Forty out of seventy plants (57%) used ethnomedically in tropical countries to treat adult onset diabetes mellitus demonstrated activity in mice with diabetes. A number of publications have described several plant species used ethnomedically to treat Type 2 diabetes mellitus in adults that have demonstrated anti-diabetic activity in rodents and in some cases humans.

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Biographical Sketches

Steven R. King is the Vice President of Ethnobotany and Conservation at Napo Pharmaceutical Inc, in South San Francisco, California, Dr. King is also a collaborator with the Institute for Ethnomedicine of the National Tropical Botanical Garden. Previously he was the Chief Operating Officer and Sr. VP of Ethnobotany and Conservation at Shaman Pharmaceuticals in charge of international relations, field research, conservation and long term supply of plant material for all of Shaman's research and development activities. He and Dr. Limbach contributed to the ethnomedical and ethnobotanical type 2 diabetes research and development program at Shaman Pharmaceuticals Inc. Dr. King has conducted ethnobotanical and ethnomedical field research in 15 countries in Latin America, Africa and South East Asia.

Charles F. Limbach, MD is a medical doctor specialized in Family Practice. He began working with ethnomedicine in 1990. Dr. Limbach helped develop the basic field screening techniques described in this chapter. He has performed Ethnomedical field reseqrch in Africa and South America and served as a Scientific Advisor to Shaman Pharmaceuticals for several years. Dr. Limbach is bilingual and currently provides health care services to Mexican migrant workers and other medically indigent people in central California.