USE OF PLANT BASED MEDICAMENTS IN TREATMENT OF METABOLIC DISORDERS: DIABETES MELLITUS

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Diabetes mellitus is a metabolic disorder that results in hyperglycemia due to decreased insulin production or inefficient insulin utilization. This disease has been reported in animals, particularly in aged dogs. However, the disorder is much more prevalent in humans. Millions of people across the globe currently have diabetes and incidence rates are predicted to increase dramatically as the population ages. The high cost of diabetes, has led to a growing interest in alternative therapies for diabetes management.

Several botanical supplements have been studied as potential therapeutic agents in the management of diabetes and its related complications. Hundreds of plant species have been studied for their potential blood glucose lowering properties. The better studied botanicals with hypoglycemic activity include Momordica charantia (bitter melon), Trigonella foenum-gracum (fenugreek), Gymnema sylvestre (gurmar), Panax quinquefolius (ginseng), Opuntia streptacanthia (nopal cactus), Aloe barbadenesis (aloe), Vaccinium mytillus (bilberry), Silybum marianum (milk thistle), Allium sativum and Allium cepa (garlic and onions) and Pterocarpus marsupium (Vijayasar).

***Momordica charantia* (bitter melon)**

Momordica charantia, also referred to as bitter melon, bitter gourd and karela, is a member of the Curcurbitaceae family and is commonly used as a traditional remedy for diabetes in India, Asia, Africa and South America. The fruit, leaf and stem of the plant have all been used to make diabetic decoctions, although it is the fruit, or the juice of the fruit, that have been studied in a research setting. Compounds isolated from the fruit and seeds of the plant that are believed to contribute to its hypoglycemic activity include charantin (a steroid glycoside) and polypeptide “p” or plant insulin (a 166 residue insulinomimetic peptide). Other bioactive peptides have also been isolated from Momordica. Momordica has been hypothesized to act via both pancreatic and extrapancreatic mechanisms with decreased hepatic glucose output, increased glucose uptake and utilization by peripheral tissues, decreased intestinal glucose absorption and increased muscle glycogen synthesis.

Momordica has been studied in several human clinical trials. These studies suggest potential benefit of Momordica but inadequacies in study design (lack of randomization, inadequate placebo or control groups and short duration of trial) limit the usefulness of the data at this time. Studies using an extract or juice from the bitter melon fruit and powdered bitter melon have been conducted in subjects with type 2 diabetes and two clinical trials investigated the effects of injected polypeptide “p” in subjects with both insulin and non-insulin dependent diabetes. Decreases in fasting blood glucose, hemoglobin A1c and postprandial blood glucose ranged between 15-42%. Animal research suggests that viable beta-cell function may be required for hypoglycemic activity and human studies show that there are both responders and non-responders among subjects with type 2 diabetes. Human clinical trials suggest liquid extracts ofthe fruit are more effective than the powdered dried fruit.

Lack of standardization of products makes determination of an effective dose difficult but research studies have used 50-200 ml/day of the fresh juice, 3-15 grams of the dried powdered fruit or 300-600 mg of a standardized extract. There are no long term studies on the use or safety of bitter melon but it is commonly used as a cooked vegetable in India and is generally believed to be safe. Potential side effects of the fruit include hypoglycemia (especially when used in combination with hypoglycemic medications and insulin), increased uterine bleeding and contractions, and hepatotoxicity. The arils around the seeds contain a toxic compound, which has been implicated in at least one death.

***Trigonella foenum-gracum* (fenugreek)**

Fenugreek is commonly used as a spice in cooking and in small quantities is categorized as “Generally Recognized As Safe” by the U.S. Food and Drug Administration. Fenugreek is a member of the Leguminosae (Fabaceae) family and is commonly cultivated in India, Egypt, the Middle East and North Africa. The seeds of the plant have been used as a traditional remedy for numerous conditions including gastrointestinal disorders, gout, wound healing and inflammation, hyperlipidemia and diabetes.

Bioactive compounds isolated from fenugreek seeds include saponins (ie: fenugreekine, diosgenin), alkaloids (ie: trigonelline, gentianine, carpaine), amino acids, some of which act as insulin secretogogues (ie: 4-hydroxyisoleucine, arginine), coumarins, mucilaginous fibers (galactomannan), nicotinic acid and other vitamins and minerals. Much of the hypoglycemic effect of fenugreek seeds in clinical studies is likely due to the inhibitory effects of mucilaginous fibers on glucose absorption. In one study subjects receiving fenugreek were consuming approximately 80 grams of fiber per day, although additional effects of fenugreek on glucose uptake and utilization have been noted in peripheral tissues. Fenugreek has also been shown to improve dyslipidemia in subjects with diabetes.

Clinical studies of fenugreek have been conducted in subjects with both type 1 and type 2 diabetes. In many cases inadequate descriptions of study design (randomization, blinding) and patient characteristics make it difficult to assess the quality of the research. But in general, studies have shown a decrease in both fasting (up to 30%) and postprandial blood glucose levels (20-35%), hemoglobin A1c (12%), and in some cases cholesterol and triglyceride levels.

Typical doses of fenugreek used in research studies have varied a great deal (5-100 g/day) Studies using higher doses have incorporated powdered fenugreek seed into foods such as bread products. Research studies using fenugreek have reported few significant side effects with use up to six months. Side effects associated with high doses of fenugreek are primarily gastrointestinal in nature, cramping, diarrhea and flatulence, but uterotonic properties and hypersensitivity reactions have also been noted. In addition fenugreek may alter the absorption of medications taken concurrently due to its high fiber content and may enhance anticoagulant medications and interact with MAO inhibitors and hypoglycemic medications.

***Gymnema sylvestre* (gurmar)**

Gymnema sylvestre, also called gurmar, has been used as a traditional treatment for diabetes in India. It is a member of the Aclepiadaceae (milkweed) family. The leaf when chewed is reported to decrease the ability of the taste buds to detect sweet tastes, hence the traditional name gurmar or “sugar destroyer”. In addition gymnema is reported to increase glucose uptake and utilization and improve the function of pancreatic beta cells (the cells which produce insulin). Gymnema may also decrease glucose absorption in the gastrointestinal tract.

The active constituents of gymnema are believed to be gymnemic acids (a mixture of acid-insoluble triterpenoid saponins) sterols (stigmasterol, quercitol) and amino acid derivatives (betaine, trimethylamine, choline). Research using pancreatectomized animals found no effect of gymnema supplementation, suggesting that some degree of beta cell function may be necessary for gymnema’s effects.

Gymnema has been studied in human clinical trials using subjects with both type 1 and type 2 diabetes. Again, research study design has not been optimal, leaving important questions as to gymnema’s effectiveness. In these studies gymnema decreased both fasting blood glucose levels and hemoglobin A1c levels. In subjects using insulin, insulin requirements were also decreased. It has been reported that gymnema generally decreases fasting blood glucose levels by 19-35%, postprandial blood glucose levels by up to 21% and hemoglobin A1c by 29-35%.

Typical doses of gymnema range between 400-600 mg/d of a standardized extract (standardized to 24% gymnemic acids) usually provided in divided doses. Gymnema has no known toxic effects and has been used for up to 30 months in research studies. It does have the potential to cause hypoglycemia and may interact with other hypoglycemic medications.

Animal studies report that gymnema can lower blood sugar levels. Preliminary human research reports that gymnema may be beneficial in patients with type 1 or type 2 diabetes when it is added to diabetes drugs being taken by mouth or to insulin. Further studies of dosing, safety, and effectiveness are needed before a strong recommendation can be made.

Reductions in levels of serum triglycerides, total cholesterol, and low-density lipoprotein ("bad cholesterol") have been observed in animal studies. Preliminary research in people with type 2 diabetes reports decreased cholesterol and triglyceride levels. Better evidence is needed before a clear conclusion can be drawn.

***Panax quinquefolius* (ginseng)**

The term ginseng is used to refer to several distinct plant species with differing effects. American (Panax quinquefolius) and Asian or Korean ginseng (Panax ginseng) belong to the Panax family (Aralicaea) of ginseng and are believed to have more similar effects than Siberian ginseng (Eelutherococcus senticosus), which is not a “true” ginseng. Ginseng is one of the most widely purchased herbal supplements in the United States and is purported to act as an “adaptogen,” improving the body’s ability to respond to illness and stress. It is reported to improve stamina, cognitive function and general well-being. These effects are not clearly supported by clinical research studies.

Panax ginseng root has been studied in two studies in subjects with type 2 diabetes. Study design was better than for other botanical products with placebo controls, blinding and randomization utilized. Ginseng supplements significantly improved fasting blood glucose level (11%), hemoglobin A1c (8%) and postprandial blood glucose levels (22%). It has been hypothesized based on animal research that ginseng may alter GI absorption of glucose, increase glucose transporter number and glucose uptake and increase insulin release. The active constituent of ginseng root is reported to be a mixed group of ginsenosides or panax glycans, many of which appear to have opposing physiological effects. Other compounds in ginseng may also contribute to its biological activity and include various vitamins, sterols, peptides, adenosine and flavonoids .

The dose of ginseng used in clinical trials in subjects with diabetes varied widely with one using three grams per day and another 100-200 mg/day. Typical doses of ginseng used for other purposes range between 100-600 mg/day standardized ginseng extract in one to two doses . There

are no long term studies of its effects in people with diabetes. Side effects of high doses of ginseng include excitation, insomnia, nervousness, diarrhea, chest pain, headache, hypertension and estrogenic effects including vaginal bleeding . These effects are generally dependent on the dose and duration of use. Ginseng has also been reported to interact with several medications including MAO inhibitors, anticoagulants, diuretics, stimulants and hypoglycemic medications.

Several human studies report that ginseng may lower blood sugar levels in patients with type 2 diabetes, both at fasting states and after eating. Long-term effects are not clear, and it is not known what doses are safe or effective. Preliminary research suggests that ginseng may not carry a significant risk of causing dangerously low blood sugar levels (hypoglycemia). Additional studies are needed that measure long-term effects of ginseng in diabetes patients, and which examine interactions with standard prescription drugs for diabetes. People with diabetes should seek the care of a qualified healthcare practitioner, and should not use ginseng instead of more proven therapies. Effects of ginseng in type 1 diabetes ("insulin dependent") are not well studied.

***Opuntia streptacantha Lemaire* (nopal cactus)**

Opuntia streptacantha Lemaire, also referred to as nopal and prickly pear cactus, is a member of a family of cacti commonly used as a food source and medicinal plant in Central and South America. Both the sap and the leaves of the cactus Opuntia streptacanthia Lemaire have been studied for their blood glucose lowering properties in animal models or subjects with type 2 diabetes. There are no research studies in people with type 1 diabetes. Opuntia may also decrease blood lipid levels .

The use of Opuntia streptacantha Lemaire as a treatment for diabetes has been tested in several small clinical trials in subjects with type 2 diabetes. Studies generally have not been well designed with few subjects and in many cases lack of randomization, blinding or placebo controls. Positive effects on postprandial blood glucose have been noted with maximal decreases in plasma glucose levels of 20-40 mg/dl (10-20%) two to four hours after consumption of nopal and decreases of up to 63 mg/dl after 10 days nopal consumption .

The exact mechanism by which nopal decreases blood glucose is unknown. Because nopal is a good source of fiber and pectin it is believed to act primarily by decreasing glucose absorption in the gastrointestinal tract. Nopal may also improve insulin sensitivity in peripheral tissues.

Most studies have used intact cooked or fresh nopal but extracts of the plant have also been used. A typical dose is 500 grams of nopal eaten before or with the meal. There are no known serious side effects associated with the use of nopal. Minor side effects are primarily GI in nature and likely due to an increase in dietary fiber. Nopal should not be taken with other medications as it may alter their absorption.

***Aloe barbadenesis* (aloe)**

Aloe barbadenesis, more commonly known as aloe vera, is one of several hundred plants of the Lilliacael family referred to as “aloe.” Aloes have been used as medicinal plants for centuries, most commonly as a topical agent used to enhance wound healing . Two forms of aloe extracts are available, aloe gel and aloe juice. Aloe juice is a bitter sap that contains anathraquinones, which have strong laxative effects. Aloe gel is a mucilaginous extract, which contains the polysaccharide glucomannan. Aloe gel does not contain anathraquinones although total leaf extracts do . Aloe gel has been used orally as a treatment for type 2 diabetes and hyperlipidemia.

The active components of aloe gel are not known but may include mucilaginous polysaccharides (including glucomannan), vitamins, minerals (including chromium), saponins, B-sitosterol, salicylic acids and amino acids3. Oral use of aloe gel decreased fasting blood glucose (by more than 100 mg/dl) and hemoglobin A1c levels in three uncontrolled studies of people with type 2 diabetes . Triglyceride levels also decreased.

Typical doses or oral aloe gel used for treatment of type 2 diabetes ranged between 1/2 teaspoon twice daily to 1 tablespoon daily . There were no adverse effects reported with the use of aloe although theoretical concerns include additive hypoglycemia in subjects using hypoglycemic medications and potential diarrhea and potassium loss due to contamination of aloe gel with anathraquinones . Oral aloe may interact with several cardiac medications, diuretics and steroids and can stimulate uterine contractions.

Laboratory studies show that aloe can stimulate insulin release from the pancreas and can lower blood glucose levels in mice. Results from two poorly conducted human trials suggest that oral aloe gel may be effective in lowering blood glucose levels, although a third, smaller study found no effect. More research is needed to explore the effectiveness and safety of aloe in diabetics.

***Vaccinium mytillus* (bilberry)**

Vaccinium mytillus, also referred to as bilberry or European blueberry, is a close relative of North American blueberry and huckleberry . The leaves have been used in traditional teas for

diabetes and in animal studies extracts from bilberry leaves decreased blood glucose and blood triglyceride levels. The berry of the plant has been used to improve visual acuity and night vision and has been studied in animals as a treatment for diabetic retinopathy. A recent well controlled clinical trial did not show any benefit on night visual acuity or contrast sensitivity in healthy, young, male subjects with normal vision.

Bilberry fruit is a rich source of anthocyanosides, a class of bioflavonoids that are believed to be responsible for the berry's therapeutic properties. Bilberry extracts typically contain 25% anthocyanosides (at least 15 different types), tannins and other flavonoids . Anthocyanosides are reported to increase vascular permeability, improve microvascular circulation, decrease platelet aggregation and improve retinal regeneration . The anthocyanoside myritillin has also been proposed as a hypoglycemic agent. The leaf of the bilberry plant has also been used as a component of "diabetic" teas and is a rich source of chromium. High doses of bilberry leaves (greater than 480 mg/day) can be toxic .

Bilberry has been used traditionally in the treatment of diabetes, and animal research suggests that bilberry leaf extract can lower blood sugar levels. Human research is needed in this area before a recommendation can be made.

***Silybum marianum* (milk thistle)**

Silybum marianum, or milk thistle, is a member of the aster (Asteraceae or Compositae) family . It is believed to have hepatoprotective effects and has been used to treat and prevent hepatotoxic reactions in alcoholic cirrhosis, viral hepatitis, mushroom and medication poisonings. It may also alter insulin resistance in patients with hepatic damage. There is one clinical trial examining the effects of 600 mg/d silymarin (one of the known active ingredients in milk thistle) in subjects with cirrhosis and type 2 diabetes. Insulin requirements, fasting blood glucose and hemoglobin A1c all declined significantly with supplementation.

A small number of studies suggest possible improvements of blood sugar control in cirrhotic patients with diabetes. However, there is not enough scientific evidence to recommend milk thistle for this use.

***Allium sativum and Allium cepa* (garlic and onions)**

Garlic and onions, best known for their cardiovascular and lipid lowering effects, have also been studied for their hypoglycemic effects. Research in humans and animals is minimal with some, but not all, initial research suggesting that members of the allium family have mild hypoglycemic activity. The active constituents are believed to be volatile sulfur-containing compounds (more than 20

have been isolated from garlic) including alliin (diallyl disulfide oxide), APDS (allyl propyl disulfide), S-allyl cysteine and S-allyl mercaptocysteine. It is hypothesized that sulfur-containing compounds in garlic decrease the rate at which insulin is degraded, effectively increasing circulating insulin levels .

***Pterocarpus marsupium* (Vijayasar)**

Pterocarpus marsupium (Leguminosae, Fabaceae) is a traditional antidiabetic plant used in Ayurvedic medicine. Concentrated extracts of the bark and the heartwood of the plant have been tested under uncontrolled conditions in subjects with type 2 diabetes. In subjects with less advanced diabetes, 2-4 grams per day of dried Pterocarpus extract decreased fasting blood glucose levels (~30 mg/dl), postprandial blood glucose (~45 mg/dl) and hemoglobin A1c (0.4%)51. Studies in animals suggest Pterocarpus may also affect lipid levels, gastrointestinal glucose absorption, improve beta-cell function and have insulin-like actions. The bioactive constituents are believed to include (-)epicatechin (a flavonoid), marsupsin (a benzofuranone), pterosupin (a dihydrochalcone) and liquiritigenin (a stilbene).

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