REVIEW ON ROLE OF NATURAL ALPHA-GLUCOSIDASE INHIBITORS FOR MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes, a state of improperly regulated homeostasis of carbohydrate and lipid metabolism is one of the major killers in recent times. Most prevalent form of diabetes is non insulin dependent diabetes mellitus (NIDDM/type II). Rapid hydrolysis of starch mediated by pancreatic α-amylase and α-glucosidases followed by glucose uptake at intestine results in sudden rise in blood glucose levels, causing hyperglycemia in type II diabetes patients. Alpha-glucosidase inhibitors act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. Natural alpha-glucosidase inhibitors such as Acarbose and Miglitol used for management of diabetes widely, but they are associated with side effects, in this review search for more natural alpha-glucosidase inhibitors are discussed which are safer as compared to insulin and other oral hypoglycaemic drugs.

KEY WORDS: Alpha-glucosidase, Insulin, Hyperglycemia, Type II diabetes

1. INTRODUCTION

Diabetes mellitus is a chronic disorder of metabolism caused by an absolute or relative lack of insulin. It is characterized by hyperglycemia (high blood sugar) in postprandial and/or fasting state, and its severe form is accompanied by ketosis and protein wasting[1], and also associated with a number of complications like retinopathy, neuropathy and peripheral vascular insufficiencies.[2] Because insulin is the principle hormone that regulates uptake of glucose into most of cells from the blood (primarily muscle and fat cells, but not central nervous system cells), deficiency of insulin or the insensitivity of its receptors plays a central role in diabetes mellitus.[3] The number of people in the world with diabetes has increased dramatically over the recent years. Indeed, by 2010 it has been estimated that the diabetic population will increase to 221 million around the world.[4] The treatment of type II diabetes is complicated by several risk factors inherent to the disease. Elevated postprandial hyperglycemia (PPHG) is one of the risk factors.[5] PPHG is elevated by the action of α-glucosidases. Alpha-Glucosidase inhibitors play a major role in managing PPHG in diabetic patients. Inhibition of alpha-glucosidase enzyme activity leads to a reduction in starch hydrolysis which

has beneficial effects on glycemic index control in diabetic patients.[6]
Traditional medicines are known to have preventive and therapeutic effects in diabetes, but their active components have not yet been characterized, except in a few cases. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated.[7]

2. MECHANISM OF ACTION OF ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestine. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels: the long term effect is a small reduction in hemoglobin level.[8]

3. HERBS WITH ALPHA-GLUCOSIDASE INHIBITORY ACTIVITY

3.1. ***Gymnema sylvestre*** (Gudmar, family-Asclepidaceae) The leaves of this plant Sarkarai kolli "sugar destroyer", 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 traditional herbs.[9]

3.2. ***Momordica charantia*** (Bitter melon, family-Cucurbitaceae) The fruits of the plant are well known in Ayurvedic medicine and in folk use as being useful in diabetes management. *M. charantia* is a proven hypoglycemic agent. In controlled clinical studies, *M. charantia* extracts have been shown to significantly lower blood sugar levels, particularly in patients with Type II diabetes. In view of these effects, *M. charantia* is a potential herbal alternative in diabetes management, particularly in non-insulin dependent diabetes. An alpha-glucosidase inhibitory activity was found in aqueous methanol extracts of the seeds of *M. charantia.*[10]

3.3. ***Trigonella foenum graecum*** (Fenugreek, family- Leguminosae) the seeds are commonly used as spice and contains 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 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. Mucilaginous substances from Fenugreek have alpha-glucosidase inhibitory activity.[11]

3.4. ***Pterocarpus marsupium*** (Vijayasar, family- Leguminosae) it is a large tree that commonly grows in the central, western, and southern parts of India and in Sri Lanka. The bark of the plant reduces the blood sugar level. The bark of the plant shown hypoglycemic activity and improve lipid profile of diabetic rats.[12] Its main compound responsible for antidiabetic activity is (-) Epicatechin and found to be insulinogenic.[13]

3.5. ***Murraya koenigii***: (Curry patta, family-Rutaceae), is an aromatic pubescent shrub or small tree commonly known as 'curry patta' in India. The extracts of *M. koenigii* leaves exhibited antihyperglycaemic as well as antioxidant activity in experimental rats and it was observed that antioxidant potential of *M. koenigii* may be responsible for its anti-diabetogenic properties.[14] Mahanimbine isolated from *M. koenigii* leaves shows antidiabetic and hypolipidemic activity in streptozotocin-induced diabetic rats.[15]

3.6. ***Ocimum sanctum*** (Tulsi, family-Lauraceae), used in Traditional Siddha system for over 2000 years has now been explored as an adjunct to dietary therapy and drug treatment in mild to moderate Type II diabetes.[16]

3.7. ***Tinospora cordifolia*** (Seenthil, family- Menispermaceae) The beneficial effects of this plant in diabetes management are well documented in traditional medicine. Recent research reveals that these effects observed in pre clinical studies can be attributed to the bitter principle isolated from the water extract. This principle has been shown to enhance insulin secretion and improve glucose metabolism, thereby lowering blood sugar levels. Saponarin, isolated from *Tinospora cordifolia* possess alpha-glucosidase inhibitory activity.[17]

3.8. ***Szygium cumini*** (*Eugenia jambolana,* family-Myrtaceae) The fruit kernels of this plant (Naval) are used traditionally in the management of diabetes. Several pre clinical studies revealed that extracts from the plant promote insulin secretion in isolated islets of Langerhans and lower blood sugar levels in experimental diabetes. The whole fruit powder is traditionally used in mixed formulations for diabetes management. In vitro studies of seed extracts of *Syzygium cumini* using the mammalian alpha-glucosidase from rat intestine showed the extracts to be more effective in inhibiting maltase when compared to the acarbose control.[18]

3.9. ***Zingiber officinale*** (Ginger, family-Zingiberaceae) is widely used as spice. For centuries ginger has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicine. Ginger juice exhibits hypoglycaemic activity in both normal and streptozotocin (STZ)-induced diabetic rats.[19]

3.10. ***Allium sativum*** (Garlic, family-Liliaceae) is oldest of all cultivated plants and has been used as medicinal agent for thousands of years as antimicrobial, antithrombic, hypolipidemic,

hypoglycemic and antitumour activity.[20] S-allyl cysteine sulphoxide isolated from *A. sativum* have antidiabetic effects in alloxan diabetic rats.[21]

Lifestyle management including diet control and adequate exercise is essential to the successful treatment of Type II diabetes. Experts on diet and health and the American Diabetes Association (ADA) state that there is no single dietary regimen for diabetes. Dietary recommendations may be developed based on the individuals requirements and treatment goals. Successful nutritional management of diabetes entails.

• Regular monitoring of metabolic parameters (including blood glucose, glycated hemoglobin, lipids, and blood pressure) In long term patients monitored the blood urea and serum creataine
• Maintaining healthy body weight
• Lifestyle management

4. DISCUSSION

There are many reports of herbal extracts being used in Ayurvedic literature as antidiabetic which are directly or indirectly used for the preparation of many modern drugs. However, these plants have not gained much importance as medicines and one of the factors is lack of specific standards being prescribed for herbal medicines and supportive animal/clinical trials.[22] Plants are known to produce a large variety of glucosidase inhibitors that provides protection against insects and microbial pathogens,[23,24] therefore plant extracts were analyzed for alpha-amylase inhibitory activity. Pancreatic and intestinal glucosidases are the key enzymes of dietary carbohydrate digestion and inhibitors of these enzymes may be effective in retarding glucose absorption to suppress PPHG. The liver glucosidase inhibitors, inhibits -1, 6-glucosidase of glycogen-debranching enzymes in the liver and reduces the glycogenolytic rate which increases the accumulation of glycogen stores in the liver.[25] Inhibition of these enzyme systems decreases the current blood glucose levels in diabetic patient (as a short term effect) and shows a small reduction in hemoglobin A1c level.[26]

5. CONCLUSION

Diabetes being multifactorial disease the treatment choice differs from patient to patient. Therefore, it is important to find out the biological activity of these herbal extracts. Theoretically, these herbs medicines act through a variety of mechanism. Presently in this review we discuss about role of alpha-glucosidase inhibitors and its role in management of diabetes type II. They can be further studied and may be used as dietary supplement for controlling PPHG in type II diabetes.

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Table 1*:* Medicinal plants with alpha-glucosidase inhibitory activity

Plant Name	Family	Part used
Aegle marmeloes	Rutaceae	Leaf, fruit
Aloe vera	Asphodelaceae	Fleshy plant
Anacardium occidentale	Anacardiaceae	Root bark
Artemisia santolina	Asteraceae	Aerial parts
Asparagas racemosus	Liliaceae	Tuber
Berberis integrimma	Berberidaceae	Aerial parts, roots
Brassica nigra	Brassicaceae	Seeds
Camellia sinensis	Theaceae	Leaves
Cannabis sativa	Cannabaceae	Seeds
Cassia auriculata	Leguminosae	Leaf, bark, flower, seed, latex
Cassia fistulla	Fabaceae	Flower
Cichorium intybus	Asteraceae	Roots

Citrus aurantium	Rutaceae	Flowers
Coccinia indica	Cucurbitaceae	Tuber
Crocus sativa	Iridaceae	Leaves
Cuminum cymirum	Apiaceae	Seeds
Eugenia jambolana	Myrtaceae	Seed, root, fruit
Ficus bengalensis	Moraceae	Bark, leaf, fruit, flower, latex
Ficus carica	Moraceae	Leaves
Foeniculum vulgare	Apiaceae	Fruits
Glycyrrhiza glabra	Fabaceae	Aerial parts
Gossypium arboreum	Malvaceae	Leaf, flower, bark, fruit
Holarina antidysentrica	Asclepidaceae	Bark, seed
Lawsonia inermis	Lythraceae	Leaves
Murraya koenigi	Rutaceae	Leaves
Nigella sativa	Ranunculaceae	Seed
Nigella sativa	Ranunculaceae	Seeds
Phyllanthus amarus	Phyllanthaceae	Whole plant
Piper nigrum	Pipereaceae	Fruits
Punica granatum	Lytheraceae	Fruits hull
Solanum dulcamara	Solanaceae	Fruits
Strychnos potatorum	Loganiaceae	Seed
Terminalia arjuna	Combretaceae	Bark
Terminalia chebulla	Combretaceae	Fruits
Tinospora cordifolia	Menispermaceae	Bark
Trigonella foenum graecum	Fabaceae	Seeds