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INVESTIGATIONS ON SOME PLANTS FOR THE MANAGEMENT OF TYPE 2 DIABETES

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ABSTRACT

Diabetes mellitus (DM) is a group of heterogeneous disorders with distinct genetic, etiologic and pathophysiological mechanisms with the common elements of glucose intolerance and hyperglycemia, due to insulin deficiency, impaired insulin action or by both. World Health Organization (WHO) report on diabetes shows that in 2014 the global prevalence of diabetes is 9% among adults aged 18+ years, majority of which are Type-II diabetics and 1.5 million deaths are resulted directly due to diabetes. These estimates are expected to increase by the year 2030. About 80 % of the total diabetic populations live in developing countries. In India, as per ICMR estimates, 40.9 million of total population are diabetic, which is expected to rise to 69.9 by 2025. A prevalence study by ICMR indicates 2.1 percent of urban population and 1.5 percent of rural population to be diabetic. Medicinal plants and formulations comprising many medicinal plants are being promoted as anti-diabetic drugs in the drug market. Although there is an intense research on the development of herbal drugs, only a small fraction of medicinal plants has been explored and validated. Therefore, this review of traditional medicinal and pharmacological uses of antidiabetic plants will provide a ground for future research.

Keywords: Antidiabetic plants, Type 2 Diabetes, *Clematis heynei*, *Solanum virginianum*

INTRODUCTION

Knowledge of diabetes dates back to centuries before Christ. The Egyptian Papyrus Ebers (1500 B.C) described an illness associated with passage of more urine. Celsus (30 B.C to 50 A.D) recognized the disease but it was not until two centuries later that another Greek physician, the renowned Areataeus of Cappodocia, gave the name diabetes (a siphon). He made the first complete clinical description, describing it as "melting down of the flesh and limbs into urine." In the 3rd and 6th centuries AD, scholars in China, Japan and in India wrote of a condition with polyuria in which the urine was sweet and sticky, although it had been known for centuries that diabetic urine tasted sweet, it remained for Willis in 1674 to add the observation "as if imbued with honey and sugar". The name diabetes mellitus (mellitus-honey) was thus established. A century after Willis, Dobson demonstrated that the sweetness was, indeed due to sugar. From the time of the earliest recorded history with diabetes, progress in the understanding of the disorder came slowly until the middle of the 19th century. However, over these centuries, gradually the course and complications of the disease were recognized. Within the past century an association was established with a disturbance in the beta cells, clustered as tiny islets of tissue in the exocrine pancreas.

These islets were first noted in fish by Brockman early in the 19th century, but they bear name of Langerhans who described them in mammals in 1869. Soon after, the German Scientists, Von Mering and Minkowski, found that surgical removal of the pancreas produced diabetes in dogs. At the turn of the century, Opie, an American, noted the beta cells in the islets to be damaged in humans leading to the disease. [1] Before tracing the biochemical changes in diabetic patients, physiologic role of insulin needs to be discussed in simple terms. Insulin is the body's signal whose concentration controls both storage and mobilization of fuels. Insulin is a polypeptide hormone produced by the beta cells of islets of Langerhans of pancreas. It has profound influence on the metabolism of carbohydrate, fat and protein. Insulin is considered as an anabolic hormone, as it promotes the synthesis of glycogen, triacylglycerols and proteins.[2] This hormone has been implicated in the development of diabetes mellitus. Human insulin (Mol.Wt. 5,734) contains 51 amino acids, arranged in two polypeptide chains.

MEDICINAL PLANTS

World Health Organization estimates that 80% of the world population uses complementary and alternative medicine (CAM) for their primary health care. Therefore, CAM, including medicinal herbs, acupuncture, moxibustion, and other therapies, is an extraordinary source of diabetes therapy. More than 400 plants and compounds are reported to show anti-diabetic activities *invitro* and/or *in-vivo*. However, information on the use of nutraceuticals and herbal supplements in the management of type II DM are limited.

ANTI-DIABETIC PLANTS

Herbal remedies in individually or in combination have been recommended in' various systems of medicines to cure various ailments. It is now known that 87% of all categorized human diseases can be cured by drugs of natural product origin particularly medicinal plants. Djomeni et al., (2006) reported the effort of root bark extract of Ceiha pentandra (Lin.) in lowering blood glucose level in streptozotocin induced diabetic rats.[3] Hussain (2002) reported that the water extract of leaves of *Azadirachta indica* significantly reduced the blood glucose level in STZ induced diabetes in rats.[4] This plant has been reported to posses' cardiovascular anti-microbial immunomodulatory, hypoglycemic and number of other effects. [5, 6] Nimbidin, an active principle isolated from seeds of Azadirachta indica was reported to be effective in reducing blood glucose in alloxan diabetic rabbits at a dose of 200mg/kg body weight.[7]

The ethyl acetate and dichloromethane extracts of stem bark of Bridelia ndellensis lower the blood glucose level in type -11 diabetic rats when fed simultaneously with glucose. [8] The hypoglycemic effects of Bridelia ferruginea leaf have been reported in alloxan induced diabetic rats. [9, 10] Gupta et ah, (2005),

reported anti diabetic effects of Annona squamosa (L.).[11] Djomeni et al. (2006) showed that ethanolic extiacts of Ceiba pentandra shows hypoglycemic effects on rats, [3] Shirwaikar et al. (2001) reported active constituents from Annona squamosa to have hypoglycemic action on STZ induced diabetic rats.[12] In addition to this, Olusola et al. (2003); Sharma et al. (1997) reported the hypoglycemic activity of Ceiba pentandra and Cesalpinia boubnducella seeds respectively.[13, 14] Kamtchouing et al. (1998); Sokeng et al. (2001) showed the protective role of Anacardium occidentals extract against STZ induced diabetes in rats. [15,16] Kochhar et al. (2005) showed some effects of traditional medicinal plants on non insulin dependent diabetes mellitus (NIDDM) patients.[17] Ali et al. (1993), Srivastava et al. (1993) showed the hypoglycemic activity of fruit pulp of Momordica charantia.[18,19] Karunanayke (1990), Khan (1998) studied on Momordica charantia as antidiabetic plants. [20,21] Ali et al. (1995), Abdel et al. (1997), Khosla (1995), Haefele (1997) reported on antidiabetic activity of Trigonella foenum-grecum. [22-25] Gomez et al. (1998), Sharma et al. (1986, 1990) studied antidiabetic effect of Fenugreek seed extract. [26-28] Bhaskar et al. (1990), Sharunugasundaram et al. (1983, 1990a, 1990b) studied on the antidiabetic effect of Gymnema sylvestes. [29-32] Maarles et al. (1995), Schultes (1960, 1962) studied on anti-diabetic plants and their active constituents. [33-35]

DIETARY SUPPLEMENTS/NUTRACEUTICALS

Raw bulb of Allium cepa and garlic has been used along with the conventional medicine to treat diabetes. There are supporting preclinical and clinical studies in the favor of hypoglycemic activities of these plants. Some of the bioactives such as S-methyl cysteine sulphoxide has been isolated from onion and its anti-diabetic activity has been supported in the diabetic rat models.[36] Fruits of Momordica charantia are widely used to treat diabetes, dry powder of the treats improved hyperglycemia and glucose tolerance in streptozotocin induced diabetic rats. Alcohol extract of the fruit has shown improvement in glucose tolerance in alloxan induced diabetic rabbits. A peptide similar in to bovine insulin has been isolated from the fruit and has clinically shown to reduce 45% fall in glucose level of diabetic subjects.[37] A clinical study has reported the hypoglycemic potential of fenugreek exerts by increasing insulin sensitivity. [38] Studies also have shown composite supplements of fenugreek and along with Emblica officinalis to consistently lower the fasting blood glucose levels and reduce the glycated hemoglobin (HbA1c) levels in diabetic patients.[39] Tea is a processed leaf product of Camellia sinensis, commonly called green tea. It has been shown that the green tea supplementation has beneficial effects on the blood glucose levels of the diabetic subjects.[40]

PLANT EXTRACTS AS ANTIDIABETIC AGENTS

Glycans of type A, B, C and D isolated from Anemarrhena asfoetida have shown to be potential hypoglycemic agents in alloxan induced diabetic rats.[41] Pinitol isolated from leaves of Bouganville aspectabilis have been shown to possess hypoglycemic activity at a very low dose (10mg/kg BW) in both diabetic and normal rats.[42] Ethanolic extract from the leaves of *Coccinia indica* shows hypoglycemic effect in rats and in human subjects by increasing the secretion of insulin and inhibiting gluconeogenetic enzymes. [43,44] Powdered seeds of *Eugenia jambolana* improve hyperglycemia both in diabetic rat models and type II diabetic subjects. The extracts of seed and fruit pulp of the plant improve cathepsin B activity and insulin secretion. [45] *Cyamopsistetra gonolobus* seeds contain galactomanan gum (guar gum which increases the viscosity of the solutions) has been exploited as dietary adjuvant to inhibit the glucose diffusion and absorption and thus to control postprandial hyperglycemia. [46] Bark of Ficus *bengalensishas* hypoglycemic effect in alloxan diabetic rabbits, rats and in humans. [47-50]

An active principle (GS4) from Gymnema sylvestre (gurmur) leaves shows hypoglycemic activity in streptozotocin induced diabetic rats by regenerating the destroyed beta cells and by inhibiting glucose uptake in the intestine. [51] Aqueous wood extract of Pterocarpus marsupium has shown regeneration of pancreatic β-cells in streptozotocin induced diabetic rats by increasing cAMP level in islets and conversion of pro-insulin into active one. Aqueous extract of the wood of this plant is used in treatment of DM. [52] An active principle was isolated from the ethanolic extract of the bark. The active principle when administered at a dose of 30mg/kg/BW. Twice daily for 4-5 days lowered blood glucose level of diabetic rats to near normal. The phenolic compound, marsupin, isolated from the heartwood shows improvement in overall diabetic condition in hyperglycemic rats and the effect was comparable to standard drug metformin.[53]

JUSTIFICATION OF THE REVIEW

Thousands of herbal medicines are used by people from every culture and various indigenous medicines are gradually being introduced into modern therapeutics. In developing countries about 80% of the people, especially the rural population, rely on the traditional medical remedies for their health care needs. In developed countries, there has been a resurgence of interest in herbal medicines due to a large extent on the preference of many consumers for products of natural origin. In view of the above aspects the present review provides profiles of plants (02 species) with traditional uses, available through literature source from various database with proper categorization according to the parts used and active phytoconstituents. This review was done with the aim of identifying and searching for new medicinal

plants with anti-diabetic activity that can be effectively used in the treatment of diabetes and its complications.

Clematis heynei

Clematis heynei is commonly known as Morvel in our region. Plant is climber occurring whole Marathwada region particularly in forest and hills. Plant is sweet, bitter, astringent not stimulant, laxative, used for leprosy, blood diseases fever, thirst, heart troubles, boils etc. Plants are climber all parts except old stem white tomentose.

Clematis species (Ranunculaceae) have been used continuously as anti-inflammatory agents by indigenous Australians. During examining the ethanol extract of C. pickeringii, C. glycinoides and C. microphylla, on COX-1, COX-2 and 5-lipoxygenase, [54] the authors found that Clematis pickeringii has activated significantly the protein expression of both PPAR-α and PPAR-γ. These results merit the study of the potential antidiabetic mechanism(s) of these species.

Clematis heynei Roxb is a somewhat woody climber very sparsely distributed in deciduous forests of Western Ghats, India. In the Indian system of medicine 'Ayurveda' this plant is used to eliminate malarial fever and headache. Roots are given orally for secretion of bile. Leaf paste is applied externally for itches, in wounds and skin allergies. The traditional medicine practitioners give the root decoction orally or small pieces placed in mouth in bilious vomiting. Leaf juice for treating boils leprosy, blood diseases and cardiac disorders. Decoction of root is given every night with boiled rice water to the children as anthelmintic.[55] Clematis species has many different pharmacological effects such as antibacterial, anti-inflammatory, antitumor, analgesic and diuretic functions.[56] Reports on the chemical components of genus Clematis have been scarce up to now and mainly refer to triterpenoid saponins. [56-59]

Solanum virginianum

Medicinal plant *Solanum virginianum* L (Synonyms: Solanum xanthocarpum Schrad. & Wendl.) is belong to the family solanaceae, commonly known as yellow berried night shade. It is coined by different vernacular name like in Marathi called as bhui ringani, Sanskrit Kantkari etc.

The antidiabetic potential of the fruit and leaves of Sx were studied previously in streptozotocin (STZ) induced diabetic rats. [60-62]

The Antihyperglycemic activity was associated with increase in plasma insulin. Though the exact mechanism of action is not known, it could be due to increased pancreatic secretion of insulin from

existing β-cells. It is known that certain alkaloids and flavonoids present in Solanum xanthocarpum exhibit hypoglycemic activity and is also known for their ability of beta cell regeneration of pancreas.[61]

The aqueous extract showed significant hypoglycemic effect in both normal and streptozotocin induced diabetic rats at dose of 100 and 200 mg/kg. The activity showed by aqueous extract was comparable to that of standard oral hypoglycemic agent glibenclamide. The experimental results indicated that it exhibited a potent blood glucose lowering property both in normal and streptozotocin induced diabetic rats. The LD50 of the extract was found to be high indicating high margin of safety.[62]

The plant is having astringent, stimulant, diuretic, pungent, bitter, digestive, expectorant, febrifuge, and laxative. In Siddha it is used in fever, cough, asthma, bronchitis, influenza, enteric fever and allergic conditions. A decoction of plant is used in gonorrhea. It promotes conception in females. The juice in combination with black pepper is prescribed in rheumatism. Stems flowers and fruits having bitter and carminative and are prescribed in burning of feet. In the Ayurveda, plant is described as pungent, bitter, digestive, and astringent. Stems, flowers, and fruits are bitter. Root decoction is used as febrifuge, diuretic, and expectorant. Charaka and Sushruta used the extract of entire plant and fruits in internal prescription for bronchial asthma, tympanitis, misperistalsis, piles, and dysuria and for rejuvenation. Kantkari Ghrita of Charaka is specific for cough and asthma. Lincture prepared from the stamens of flowers is prescribed for chronic cough in children. [63] The wholeplant is used traditionally for curing various ailments. Decoction of the plant is used in gonorrhea; paste of leaves is applied to relieve pains; seeds act as expectorant in cough and asthma; roots are expectorant and diuretic, useful in the treatment of catarrhal fever, cough, asthma and chest pain. The plant is also known to have pest repellent properties and used as a contact poison and mollusicide. Roots are one of the constituents of well-known Ayurvedic preparation “Dasmul Asava” and used as an expectorant, cough, asthma, and chest pain in Ayurvedic medicine.[63]

CONCLUSION

So herbal medication is the most commonly used alternative therapy for diabetes treatment. Alternatives are needed because of the inability of current therapies to contribute normally in the prevention of diabetes complications. The enormous costs of 85-95% of rural population in developing countries on traditional medicine for their primary health care necessitate the alternative strategies for the prevention and treatment of diabetes. Moreover herbs are known for their safety, efficacy, cultural acceptability and lesser side effects besides maintaining normally anemia in diabetics. However, their safety and efficacy need to be further evaluated by experimental and clinical studies. Preparation of standardized medicinal herbs in urgently needed for future studies and therapies. To date over 600 traditional plant treatments

for diabetes have been reported but only a small number of these have received scientific and clinical evaluation to assess their efficacy. In diabetics some herbal alternatives have proven to provide symptomatic relief and assist in the prevention of the secondary complications of the disease. Some herbs have also been proven to help in the regeneration of beta cells and in overcoming insulin resistance.

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