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REVIEW ARTICLE

Diabetes and Herbal Medicines

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ABSTRACT

Diabetes mellitus is a metabolic disorder in the endocrine system. This dreadful disease is found in all parts of the world and is becoming a serious threat to mankind health. There are lots of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported up to this date. Alternative to these synthetic agents, plants provide a potential source of hypoglycemic drugs and are widely used in several traditional systems of medicine to prevent diabetes. Several medicinal plants have been investigated for their beneficial use in different types of diabetes. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities using variety of mechanisms. A considerable number of plants were subjected to clinical trials and were found effective. Moreover, during the past few years many phytoconstituents responsible for antidiabetic effects have been isolated from hypoglycaemic plants. This paper focuses mainly on diabetes, plants used as antidiabetics in various traditional medicines, constituents isolated from these plants, various mechanisms through which herbs act against diabetes and few examples of antidiabetic formulations available in the market.

Keywords: *Diabetes, Herbal Medicines, antidiabetics, Clinical trials*

Diabetes is a chronic disorder in metabolism of carbohydrates, proteins, and fat due to absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance [1, 2]. Also, it may be defined as a disease where the body either produces little insulin/ceases to produce insulin, or becomes progressively resistant to its action [3]. It has now become an epidemic with a worldwide incidence of 5% in the general population. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025 [4]. The countries with the largest number of diabetic people in the year 2025 will be India, China and United States [5]. There are more than 30 million people with diabetes mellitus in India and the incidence is increasing [6]. Also, there are many patients in the community with undiagnosed diabetes. Decreased physical activity, increasing obesity, stress and changes in food consumption have been implicated in this increasing prevalence in the past two decades. Diabetes is being projected as the World's main disabler and killer in the next 25 years [7].

Patients with diabetes experience significant morbidity and mortality from microvascular (Retinopathy, neuropathy, nephropathy) and macrovascular complications (heart attack, stroke and peripheral vascular disease). The cost of treating diabetes and associated complications exceeds $ 100 billion per year. The complications are far less common and less severe in people who have well-controlled blood sugar levels [8]. Acute complications include diabetic ketoacidosis, nonketotic hyperosmolar coma, and diabetic coma. In case of chronic complication, chronic elevation of blood glucose level leads to damage to blood vessels. In diabetes, the resultant problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries) [8]. Microvascular disease leads to retinopathy, neuropathy and nephropathy (nephropathy leads to anaemia) [9,10]. Macrovascular disease leads to cardiovascular disease, mainly by accelerating atherosclerosis. These disorders include: (1) Coronary artery disease, leading to myocardial infarction (heart attack) or angina, (2) Stroke (mainly ischemic type), (3) Peripheral vascular disease, which contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot [8].

Diabetes and Insulin

Most of the food we eat is broken down into simple sugar called glucose. This glucose is the main source of fuel to get energy for the body. After digestion, the glucose reaches our blood stream where it is available for

body cells to utilize for energy, but insulin is needed for the glucose to get into cells. Insulin is a hormone secreted by the pancreas to transport glucose from blood into different cells of the body. If the pancreas does not produce enough insulin or the produced insulin does not work properly, the glucose cannot enter the body cells. So glucose stays in the blood cells, which makes the blood sugar level high. Diabetes is initially characterized by a loss of glucose homeostasis. The major effects of insulin on glucose, fatty acid, and amino acid metabolism and on ion flux are initiated by the attachment of the insulin molecule to a specific insulin receptor on the cell surface. This hormone receptor interaction is reversible, and the insulin molecule is not chemically altered during this contact. The hormone receptor complex is then internalized by an endocytotic mechanism. Insulin molecule eventually is metabolized, and the insulin receptor is recycled into the membrane for reusage. Thus, the body loses its main source of fuel for energy even though the blood contains high amount of glucose [7, 8]. The insulin resistance mainly happens in cell membrane where glucose is not transported to the cells for oxidation. Since glucose is not metabolized, high amount of glucose circulates in the blood. To keep the normal level of glucose in the blood, the kidney removes the extra sugar from the blood and excretes it in the urine. Since body does not utilize glucose, the body is under constant impression of hunger and that is why diabetics feel increased appetite (polyphagia) and eat more frequently. Symptoms of insulin resistance include a decreased stimulation of muscle glycogen synthesis, defects in glycogen synthesis activity, hexokinase activity and glucose uptake [11].

Diagnostic criteria for diabetes

The blood glucose levels of a healthy man are 80 mg/dLl on fasting and up to 160 mg/dL in the postprandial state. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating one of the following [6]:

fasting plasma glucose level at or above 126 mg/dL or 7.0 mmol/l.

plasma glucose at or above 200 mg/dL or 11.1 mmol/L two hours after a 75 g oral glucose load in a glucose tolerance test.

random plasma glucose at or above 200 mg/dL or 11.1 mmol/l.

Two fasting glucose measurements above 126 mg/dL or 7.0 mmol/l or random blood sugar level >200mg/dL on two occasions is considered diagnostic for diabetes mellitus. Patients with fasting sugars between 6.1 and 7.0 mmol/L (110 and 125 mg/dL) are considered to have imparied fasting glucose and patients with plasma glucose at or above 140 mg/dL or 7.8 mmol/L two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance.

Classification

Type I diabetes (Insulin-dependent diabetes), It is prevalent in 10% of diabetic patients, islet β-cell destruction usually leads to absolute insulin deficiency [3]. Patients are completely reliant upon exogenous insulin to prevent ketosis and thereby preserve life [12].

Type 2 diabetes (Non insulin-dependent diabetes), Accounts for more than 85% of cases worldwide. It is a heterogeneous type, ranging from insulin resistance to insulin deficiency [12, 13]. Also type 2 diabetes (T2D) is a multifactorial disease with both a genetic component and an important non-genetic component(s) [4].

Other specific forms, these include:

- Genetic defects of β-cell function, e.g. MODY syndromes
- Genetic defects in insulin action e.g. leprechaunism
- Diseases of the exocrine pancreas, e.g. pancreatitis
- Secondary to endocrinopathies, e.g. acromegaly
- Drug- or chemical-induced, e.g. glucocorticoids
- Infections, e.g. congenital rubella
- Uncommon forms of immune-mediated diabetes, e.g. 'Stiff Man' syndrome
- Other genetic syndromes associated with diabetes, e.g. Down's syndrome [12].

Gestational diabetes, Diabetes diagnosed in pregnancy, including pre-existing diabetes and diabetes which develops during pregnancy [12, 14].

Need and Scope of Alternative Remedies

Regardless of the type of diabetes, patients are required to control their blood glucose with medications and/or by adhering to an exercise program and a dietary plan. Insulin therapy by injection is given to those with type 1 DM and also to some patients with type 2 DM when oral hypoglycaemic drugs fail to lower blood glucose [11]. Due to modernization of lifestyle, non-insulin dependent diabetes mellitus is becoming a major health problem in developing countries. Patients with type 2 DM are usually placed on a restricted diet and are instructed to exercise, the purpose of which primarily is weight control. If diet and exercise fail to control blood glucose at the desired level, oral antidiabetic medication is prescribed [15].

Oral antidiabetic agents exert their effects by various mechanisms: (1) stimulation of beta cells in the pancreas to produce more insulin (sulfonylureas and meglitinides), (2) increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones), (3) decreasing gluconeogenesis by the liver (biguanides), and (4) delaying the absorption of carbohydrates from the gastrointestinal tract (alpha-glucosidase inhibitors). These treatments have their own drawbacks, ranging from the developing of resistance and adverse effects to lack of responsiveness in large segment of patients population. Sulfonylureas lose effectiveness for 44% of patients within six years. Also, these treatments are associated with side effects or even toxic effects (e.g., thiazolidin-

ediones may cause liver toxicity; sulphonylureas might worsen heart disease, lower the glucose below the normal range and increase the body weight gain; bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints with glucosidase inhibitors) [16,17,18]. According to literature, two-thirds of medications prescribed for use in children have not been proven safe or effective for this patient population [16]. Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently met with the disease [15].

The limitations of currently-available oral antidiabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemy have encouraged a concerted effort to discover drugs that can manage type 2 diabetes more efficiently [3]. Also, with increasing incidence of diabetes mellitus in rural population throughout the world and due to adverse effects of synthetic medicine, there is a clear need for development of indigenous, inexpensive botanical sources for anti-diabetic crude or purified drugs [19].

Herbal Remedies

As per nncient literature, more than 800 plants are reported to have antidiabetic properties [20]. Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity [21]. Medicinal plants, since times immemorial, have been used in virtually all cultures as a source of medicine. A study of ancient literature indicates that diabetes was fairly well known and well conceived as an entity in ancient India. The knowledge of the system of diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age. Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha, [22] a special food, which used to be offered at the times of yagna organized by Dakshaprajapati.

Ayurvedic antidiabetic herbs improve digestive power, increase one of the Rasas (gastric secretions); being Laghu, get easily digested in the body; and being Ruksha, decrease output of overall body fluids e.g. urine, sweat etc. Food items, which are 'madhumehaghna' (antidote), are an important underlying principle of therapy for the prameha (diabetes) patient. Food items which correct the metabolic imbalance by their action e.g. foods exhibiting 'rasa', 'katu', 'laghu', 'medaghna', properties are old cereals, roasted cereals, barley, jawar, ragi, mung dal, horsegram, tur dal, drumstick leaves, bittergourd, jamun, amla, fig, raw papaya, milk, meat of animals that live in dry region, etc. The indigenous diet may not be useful in lowering the blood sugar to the same extent as insulin and other hypoglycaemic agents do. But it has some other influences, which may be useful for the management of the disease and its complications [23]. Indian materia medica has mentioned numerous dravyas, which have been reported effective in Madhumeha [24].

Plants-based products have been popular all over the world for the centuries. In diabetes, some herbal alternatives are 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 ß-cells and in overcoming resistance. In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol-lowering action. The management of type 2 diabetes mellitus (NIDDM) is possible with the drugs that can lower the blood sugar level in one hand and restore the liver glycogen level on the other. In modern system of medicine, there is no drug, which is reported to posses both of these properties [25]. However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes and conventional drugs have been derived from the active molecules of these medicinal plants. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officianalis* and used to treat diabetes [26]. Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from herbs [16].

Antidiabetic Plants in Traditional Medicines

The NAPRALERT database lists over 1200 species of plants representing 725 genera in 183 families extending from the marine algae and fungi with antidiabetic activity. Over half of these have been used ethnopharmacologically in traditional medicine as antidiabetics, and some 50% of these traditional remedies have been studied experimentally [27]. The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed. Furthermore, an increasing reliance on the use of medicinal plants in the industrialized societies has been traced to the extraction and development of several drugs and chemotherapeutics from these plants as well as from traditionally used herbal remedies.

In Jordan, following plants are used to treat diabetes by the tribal people:

Achillea fragrantissima L., *Allium cepa* L., *Artemisia vulgaris* L., *Artemisia herba-alba* Asso., *Aloe vera* L., *Alpinia officinarum* Hance, *Brassica oleraceae* var. *capita* L., *Cephalaria syriaca* L., *Cichorium pumilium* L., *Cinnamomum zeylanicum* Blume, *Citrullus colocynthus* (L.) Kuntze, *Cucurbita maxima* Dutch., *Eryngium creticum* L., *Ferula persica* Willd, *Ferula hermonis* Boiss., *Pelargonium graveolens* L'Her. ex Ait., *Gundelia tournefortii* L., *Hibiscus sabdariffa* L., *Juniperus phoenicea* L., *Matricaria aurea* (Loefl.) Schultz-Bip., *Origanum syriacum* L., *Paronychia argentea* L., *Pistacia atlantica* Desf., *Pisum sativum* L., *Prosopis fracta* (Banks & Soland.) J.F. Macbr., *Quercus coccifera* L., *Rheum ribes* L., *Sarcopoterium spinosum* (L.) Sp., *Terminalia chebula* L., *Teucrium polium* L., *Trigonella foenum-graecum* L., *Varthemia iphionoides* Boiss, and *Zizyphus spina-christi* L. [28].

In Canada, following plants are used in the treatment of diabetes by the tribal people:

Abies balsamea (L.) Mill. *Achillea millefolium* L., *Acorus calamus* L., *Aralia nudicaulis* L., *Aralia racemosa* L., *Arisaema triphyllum* (L.), *Asarum canadense* var. *acuminatum* Ashe, *Celastrus scandens* L., *Cornus stolonifera* Michx., *Corylus cornuta* Marsh., *Dirca palustris* L., *Gaultheria procumbens* L., *Heracleum lanatum* Michx., *Juniperus communis* L., *Juniperus virginiana* L., *Kalmia angustifolia* L., *Ledum groenlandicum* Oeder., *Nuphar variegatum* Durand, *Picea glauca* (Moench) Voss., *Picea mariana* (Mill.), *Populus balsamifera* L., *Populus tremuloides* Michx., *Prunus serotina* Ehrh., *Quercus alba* L., *Quercus rubra* L., *Rhus hirta* f. *typhina* (L.), *Sassafras albidum* (Nutt.) Ness., *Smilacina racemosa* (L.) Desf., *Solidago canadensis* L., *Sorbus Americana* Marsh, *Taraxacum officinale* Weber., *Taxus canadensis* Marsh., *Thuja occidentalis* L., *Tsuga canadensis* (L.) and *Verbascum thapsus* L. [29,30].

In Morocco, the most frequently used plants to treat diabetes includes *Ammi visnaga* Lam., *Carum carvi* L., *Coriandrum sativum* L., *Foeniculum vulgare* Gaertn, *Nerium oleander* L., *Lepidium sativum* L., *Capparis spinosa* L., *Artemisia absinthium* L., *Artemisia herba alba* Asso., *Lactuca sativa* L., *Tetraclinis articulata* Benth., *Globularia alypum* L., *Lavandula dentata* L. , *Marrubium vulgare* L., *Mentha pulegium* L., *Origanum compactum* Benth., *Rosmarinus officinalis* L., *Lupinus albus* L., *Trigonella foeniculum-graecum* L., *Allium sativum* L. *Allium cepa* L., *Aloe succotrina* Lam., *Linum usitatissimum* L., *Eucalyptus globulus* Labill, *Myrtus communis* L., *Olea europaea* L., *Sesamum indicum* Dc., *Punica granatum* L., *Nigella sativa* L., *Prunus amygdalus* stokes var. amara CD., *Citrus bigaradia* Riss., *Peganum harmala* L. and *Zygophyllum gaetulum* Emb. Maire [31,32].

In Africa, following plants are used in the treatment of diabetes:

Pileostigma thonningii Milne-Redh., *Xylopia aethiopica* (Dun.) A. Rich., *Combretum micranthum* G. Don., *Ficus capensis* Thunb., *Cassia sieberiana* DC., *Nauclea pobeguinii* Petit, *Ocimum sanctum* L., *Anacardium occidentale* L., *Jatropha curcas* L., *Nauclea latifolia* Smith, *Allium sativum* L., *Citrus medica* Linn., *Moringa oleifera* Lam., *Persea americana* Mill., *Catharanthus roseus* (L.) G. Don., *Landolphia heudeloti* DC., *Tamarindus indica* L., *Afzelia africana* Smith ex Pers., *Andansonia digitata* L., *Carica papaya* L., *Euphorbia hirta* L., *Garcinia kola* Heckel, *Landolphia dulcis* (Sabine) Pichon, *Mesonerum benthamianum*, *Ocimum viridae* Willd, *Psidium guajava* L, *Pterocarpus ericens* Poir., *Scoparia dulcis* L. and *Uvaria chamae* P.Beauv. [33].

In Mexico more than 500 species are used in traditional medicine for diabetes, Among them *Abutilon lignosum* (Cav.) D. Don, *Abutilon trisulcatum* (Jacq.) Urban., *Acacia retinodes* Schltdl. , *Acourtia thurberi.* (A.Gray) Reveal & R. M.King, *Acrocomia mexicana* Karw. ex Mart., *Agastache mexicana* (Kunth) Lint et Epling, *Agave atrovirens* Karw. Ex Salm-Dyck, *Agave lecheguilla* Torr., *Agave salmiana* Otto, *Ageratina petiolaris* Moc., *Ageratum conyzoides* L., *Allionia choisyi* Standl., *Allium cepa* L., *Alloispermum integrifolium* (DC.) H.Rob., *Aloe barbadensis* Mill., *Aloe vera* (L.) Burm. F, *Ambrosia artemisiifolia* L., *Anacardium occidentale* L., *Ananas comosus* (L.) Merr., *Annona cherimola* Mill., *Annona glabra* L., *Annona muricata* L., *Apodanthera buraeavi* Cogn., *Aporocactus flagelliformis* (L.) Lem., *Arachis hypogaea* L., *Arceuthobium vaginatum* (Humb. & Bonpl. Ex Willd.), *Argemone mexicana* L., *Argemone platyceras* Link & Otto, *Aristolochia malacophylla* Standl., *Aristolochia sericea* Benth., *Artemisia absinthium* L., *Artemisia ludoviciana* Nutt., *Artemisia vulgaris* L. *Asclepias linaria* Cav., *Barosma betulina* Bartl. & H.L. Wendl. *Bauhinia divaricata* L., *Begonia heracleifolia* Schltdl. & Cham., *Berberis moranensis* Schult. & Schult. f., *Beta vulgaris* L., *Bidens aurea* (Aiton) Sherff, *Bidens leucantha* (L.) Willd., *Bidens odorata* Cav., *Bidens pilosa* L., *Bocconia arborea* S. Watson, *Puemus boldus* Molina J., *Bouvardia ternifolia* (Cav.) Schltdl., *Buddleia stachyoides* Cham. & Schltd., *Bursera simaruba* (L.) Sarg., *Cacalia decomposita* A. Gray, *Cacalia peltata* Kunth, *Calea integrifolia* (DC.) Hemsl., *Calea zacatechichi* Schltdl. , *Calliandra anomala* (Kunth) J.F. Macbr., *Capraria biflora* L., *Carica papaya* L., *Cassia fistula*L., *Cassia skinneri* Benth., *Cassia tomentosa* L., *Castela tortuosa* Liebm., *Catharanthus roseus* (L.) G. Don, *Chamaecrista hispidula* (Vahl) H.S. Irwin & Barneby, *Cirsium exicanum* DC., *Cissampelos pareira* L., *Citrus aurantifolia* (Christm.) Swingle Lim., *Citrus limetta* Risso, *Citrus sinensis* (L.), *Cordia tinifolia* Willd., *Coriandrum sativum* L., *Costus mexicanus* Liebm., *Croton draco* Schltdl., *Cucurbita maxima* Duchesne, *Cuscuta jalapensis* Schltdl., *Cynara scolymus* L., *Cynodon dactylon* (L.) Pers., *Daucus carota* L., *Eucalyptus globules* Labill, *Euphorbia maculata* L., *Euphorbia prostrata* Aiton, *Foeniculum vulgare* Mill., *Fraxinus alba* Marshall, *Guaiacum coulteri* A. Gray, *Guaiacum sanctum* L., *Hibiscus rosa-sinensis* L., *Ipomoea starts* Cav. , *Jatropha dioica* Cerv., *Jatropha elbae* J., *Kalanchoe pinnata* (Lam.) Pers., *Mentha piperita* L., *Mentha rotundifolia* (L.) Huds., *Mentha suaveolens* Ehrh., *Momordica charantia* L., *Musa sapientum* L., *Olea europaea* L, *Opuntia atropes* Rose, *Persea americana* Mill., *Physalis philadelphica* Lam.., *Piper auritum* Kunth, *Piper hispidum* Sw., *Plantago australis* Lam., *Plantago major* L.,. *Plumbago scandens* L., *Plumeria rubra* L., *Psidium guajava* L., *Psidium yucatanense* Lundell, *Quassia amara* L., *Quercus acutifolia* Nees, *Raphanus sativus* L., *Ricinus communis* L., *Senecio peltiferus* Hemsl., *Senna multiglandulosa* (Jacq.) H.S. Irwin & Barneby, *Senna obtusifolia* L., *Senna occidentalis* L., *Tagetes erecta* L., *Tamarindus indica* L., *Terminalia catappa* L., *Trigonella foenum-graecum* L., *Urtica dioica* L., *Valeriana edulis* Nutt., *Zea mays* h., *Zizyphus acuminate* Benth, etc are the important ones [34].

In China, the following species are commonly used for diabetes in traditional medicine:

Astragalus membranaceus (Fisch.) Bunge, *Astragalus membranaceus* (Fisch.) Bunge, *Rehmannia gluti-*

nosa Libosch., *Trichosanthes kirilowii* Maxim., *Pueraria lobata* (Willd.) Ohwi., *Panax ginseng* C.A. Mey., *Panax quinquefolium* L., *Polygonatum sibiricum* Red., *Polygonatum odoratum* (Mill.) Druce., *Cornus officinalis* Sieb. et Zucc., *Whitmania pigra* Whitman, *Coptis chinensis* Franch., *Lycium barbarum* L., *Poria cocos* (Schw.) Wolf., *Atractylodes lancea* (Thunb.) DC., *Anemarrhena asphodeloides* Bunge., *Ophiopogon japocicus* (Thunb.) Ker-Gawl., *Ligustrum lucidum* Ait., *Morus alba* L., *Schisandra chinensis* (Turcz.) Baill., *Gynostemma pentaphyllum* (Thunb.) Mak., *Salvia miltiorrhiza* Bunge., *Phragmites communis* Trin., *Alisma orientale* (Sam.) Juzep., *Cuscuta chinensis* Lam., *Epimedium sagittatum* (Sieb. et Zucc.) Maxim., *Clematis chinensis* Osbeck, *Panax notoginseng* (Burk.) F. H. Chen, *Dendrobium nobile* Lindl., *Ostrea gigas* Thunberg, *Ostrea talienwhanensis* Crosse, *Ostrea rivularis* Gould., *Lithospermum erythrorhizon* Sieb. et Zucc., *Aconitum carmichaeli* Debeaux., *Paeonia veitchii* Lynch, *Rheum palmatum* L., *Rheum officinale* Baill., *Pinellia ternata* (Thunb.) Breit., *Polygala tenuifolia* Willd., *Hordeum vulgare* L., *Phellodendron amurense* Rupr., *Arctium lappa* L., *Xanthium sibiricum* Patr., *Bombyx mori* L., *Gekko gekko* L., *Polygonum cuspidatum* Sieb. et Zucc., *Codonopsis pilosula* (Franch.) Nannf., *Scrophularia ningpoensis* Hemsl., *Ligusticum chuanxiong* Hort., *Momordica charantia* L., *Punica granatum* L., *Dioscorea opposita* Thunb., *Allium sativum* L., *Zea mays* L., *Fagopyrum cymosum* (Trev.) Meisn., *Allium cepa* L., *Asparrausi officinalis* L., *Gymnema sylvestre* (Retz.) Schult, *Trigonella foenum-graecum* L., *Prunella vulgaris* L. and *Ephedra sinica* Stapf., etc [35].

In Israel, 26 species are reported to be used in the treatment of diabetes by the tribal people:

Achillea fragrantissima (Forssk.) Sch. Bip., *Achillea millefolium* L., *Allium cepa* L., *Artemisia herba-alba* Asso., *Capparis iberica* Trevir. ex Spreng., *Ceratonia siliqua* L., *Coridothymus capitatus* (L.) Rchb. F., *Crataegus azarolus* L., *C. sempervirens* L., *Juglans regia* L., *Lupinus varius* Gaertn, *Melissa annua* L., *Morus nigra* L., *Olea europaea* L., *Pinus halepensis* Mill., *Prosopis farcta* (Sol. Ex Russell) J.F. Macbr., *Q. calliprinos* Decne, *Salvia fruticosa* Mill., *Sarcopoterium spinosum* (L.) Spach, *Silene aspera* L., *Teucrium polium* L. and *Trigonella foenum- graecum* L. are the important ones [36].

Plant species used in the treatment of diabetes by the people of North American forest are:

Abies balsamea (L.) Mill., *Achillea millefolium* L., *Acorus calamus* L., *Aralia nudicaulis* L., *Aralia racemosa* L., *Arisaema triphyllum* (L.) Schott., *Asarum canadense var. acuminatum* Ashe, *Celastrus scandens* L., *Cornus stolonifera* Michx., *Corylus cornuta* Marsh,. *Dirca palustris* L., *Gaultheria procumbens* L., *Heracleum lanatum* Michx., *Juniperus communis* L., *Juniperus virginiana* L., *Kalmia angustifolia* L., *Ledum groenlandicum* Oeder., *Nuphar variegatum* Durand, *Picea glauca* (Moench) Voss, *Picea mariana* Mill, *Populus balsamifera* L., *Populus tremuloides* Michx., *Prunus serotina* Ehrh., *Quercus alba* L., *Quercus rubra* L., *Rhus hirta* L., *Sassafras albidum* (Nutt.) Nees., *Smilacina racemosa* (L.)Desf., *Solidago canadensis* L., *Sorbus americana* Marsh., *Taraxacum officinale* Weber., *Taxus canadensis* Marsh., *Thuja occidentalis* L., *Tsuga canadensis* (L.) Carr. and *Verbascum thapsus* L [37].

In India, plants like *Abroma augusta* (L.) L.f., *Abutilum indicum* (L.) Sw., *Aconitum palmatum* D. Don., *Aloe barbadensis* Mill, *Asparagus racemosus* Willd., *Berberis aristata* DC., *Calamus rotang* (L.), *Cannabis sativa* (L.), *Catharanthus roseus* (L.) G. Don., *Cinnamomum tamala* (Buch.-Ham.) Nees, *Coccinea grandis* (L.) Voigt., *Costus speciosus* (Koening) Sm., *Ficus racemosa* (L.), *Ipomoea batatus* (L.) Lamk., *Momordica chrantia* (L.), *Nardostachys jatamansi* DC., *Picrorhiza kurrooa* Royle ex Benth., *Quercus lanata* Sm., *Swertia chirayita* (Roxb. ex Flem.) Karst., *Syzygium cuminii* (L.) Skeels, *Trigonella foenum-graecum* (L.), *Urtica dioica* (L.), *Zingiber officinale* Rosc., *Allium cepa* L., *Allium sativum* L., *Aloe vera* (L.) Burm.f., *Cajanus cajan* (L.) Millsp., *Coccinia indica* Wight & Arn., *Caesalpinia bonducella* (L.) Roxb., *Ficus bengalensis* L., *Gymnema sylvestre* R. Br., *Momordica charantia* L., *Ocimum sanctum* L., *Pterocarpus marsupium* Roxb., *Tinospora cordifolia* (Willd.) Hook.f. & Thomson, etc., are most commonly used species in traditional medicine as antidiabetic agents [38,39].

Scientifically Validated Antidiabetic Plants

Among the traditional plants used for diabetes, only a small number of these have received scientific and medical evaluation as follows:

Acacia arabica (Lam.) Muhl. ex Willd. (Family: Mimosaceae), *Aegle marmelos* (L.) Correa ex Roxb. (Family: Rutaceae), *Allium cepa* L. (Family: Liliaceae), *Allium sativum* L. (Family: Alliaceae), *Aloe vera* (L.) Burm.f. (Family: Aloaceae), *Anthemis mobilis* Linn. (Family: Compositae), *Areca catechu* L. (Family: Arecaceae), *Artemisia pallens* Wall. ex DC. (Family: Compositae), *Annona squamosa* L. (Family: Annonaceae), *Andrographis paniculata* Nees (Family: Acanthaceae), *Aerva lanata* (L.) Juss. ex Schult. (Family: Amaranthaceae), *Asteracantha longifolia* Nees (Family: Acanthaceae), *Azadirachta indica* A. Juss. (Family: Meliaceae), *Biophytum sensitivum* (L.) DC. (Family: Oxalidaceae), *Bombax ceiba* L. (Family: Bombacaceae), *Beta vulgaris* L. (Family: Chenopodiaceae), *Brassica juncea* (L.) Czern. (Family: Brassicaceae), *Barleria lupulina* Lindl. (Family: Acanthaceae), *Boerhavia diffusa* L. (Family: Nyctaginaceae), *Brickellia veronicaefolia* A. Gray (Family: Asteraceae), *Cassia auriculata* L. (Family: Leguminosae), *Caesalpinia bonducella* (L.) Roxb. (Family: Cesalpinaceae), *Capparis decidua* (Forsk.) Edgew. (Family: Capparidaceae) *Cajanus cajan* (L.) Millsp. (Family: Fabaceae), *Citrullus colocynthis* (L.) Schrad. (Family: Cucurbitaceae), *Coccinia indica* Wight & Arn. (Family: Cucurbitaceae), *Casearia esculenta* Roxb. (Family: Flacourtiaceae), *Catharanthus roseus* (L.) G. Don. (Family: Apocynaceae), *Camellia sinensis* Kuntze (Family: Theaceae), *Coriandrum sativum* L. (Family: Apiaceae), *Cuminum cyminum* L. (Family:

Apiaceae), *Daucus carota* L. (Family: Apiaceae), *Eugenia uniflora* L. (Family: Myrtaceae), *Eugenia jambolana* L. (Family: Myrtaceae), *Eucalyptus globulus* Labill. (Family: Myrtaceae), *Enicostemma littorale* Blume (Family: Gentiaceae), *Ficus bengalensis* L. (Family: Moraceae), *Gymnema montanum* Hook.f. (Family: Asclepiadaceae), *Gymnema sylvestre* R. Br. (Family: Asclepiadaceae), *Glycyrrhiza glabra* L. (Family: Fabaceae), *Hibiscus rosa sinensis* L. (Family: Malvaceae), *Helicteres isora* L. (Family: Sterculiaceae), *Ipomoea batatas* (L.) Lam. (Family: Convolvulaceae), *Lantana camara* L. (Family: Verbenaceae), *Mangifera indica* L. (Family: Anacardiaceae), *Memecylon umbellatum* Burm. f. (Family: Melastomataceae), *Momordica cymbalaria* Fenzl ex Naudin (Family: Cucurbitaceae), *Mucuna pruriens* (L.) DC. (Family: Leguminosae), *Musa sapientum* L. (Family: Musaceae), *Momordica charantia* L. (Family: Cucurbitaceae), *Morus alba* L. (Family: Moraceae), *Murraya koeingii* (L.) Spreng. (Family: Rutaceae), *Nelumbo nucifera* Gaertn. (Family: Nymphaeaceae), *Ocimum sanctum* L. (Family: Lamiaceae), *Panax ginseng* Mey. (Family: Araliaceae), *Picrorrhiza kurroa* Royle ex Benth. (Family: Scrophulariaceae), *Phyllanthus amarus* Schumach. & Thonn. (Family: Euphorbiaceae), *Pterocarpus marsupium* Roxb. (Family: Fabaceae), *Punica granatum* L. (Family: Punicaceae), *Psacalium peltatum* Cass. (Family: Asteraceae), *Psacalium decompositum* Cass. (Family: Asteraceae), *Pterocarpus santalinus* L. f. (Family: Leguminosae), *Salacia reticulata* Wight. (Family: Celastaceae), *Salacia oblonga* Wall. (Family: Celastaceae) *Swertia chirayita* (Roxb. ex Fleming) H. Karst. (Family: Gentianaceae), *Scoparia dulcis* L. (Family: Scrophulariaceae), *Syzygium alternifolium* Walp. (Family: Myrtaceae), *Sida cordifolia* L. (Family: Malvaceae), *Trigonella foenum graecum* L. (Family: Fabaceae), *Terminalia catappa* L. (Family: Combretaceae), *Terminalia pallida* Brandis (Family: Combretaceae), *Tinospora cordifolia* (Willd.) Hook.f. & Thomson (Family: Menispermaceae), *Zingiber officinale* Roscoe (Family: Zingiberaceae), *Zizyphus sativa* Gaertn. (Family: Rhamnaceae), etc., are the important ones [39,40,41,42].

Plant Families Reported for Antidiabetic Activity

Various plants belonging to number of families have been reported to have antidiabetic activity. Following are few important examples of such families:
Acanthaceae, Amaranthaceae, Anacardiaceae, Apiaceae, Apocynaceae, Araliaceae, Arecaceae, Asclepiadaceae, Asteraceae, Bignoniaceae, Bombacaceae, Boraginaceae, Brassicaceae, Bromeliaceae, Buddleaceae, Cactaceae, Capparidaceae, Caryophyllaceae, Compositae, Chenopodiaceae, Convolvulaceae, Crassulaceae, Cucurbitaceae, Cupressaceae, Discoreaceae, Equisetaceae, Euphorbiaceae, Fabaceae, Geraniaceae, Gnetaceae, Gramineae, Gentianaceae, Ginkgoacea, Globulariaceae, Guttifere, Hippocastanaceae, Hippocrateaceae, Juglandaceae, Labiatae, Lamiaceae, Leguminosea, Liliaceae, Logoniaceae, Lycopodiaceae, Lythraceae, Malvaceae, Melastomaceae, Meliaceae, Menispermaceae, Moraceae, Myrsinaceae, Myrtaceae, Musaceae, Nyctaginaceae, Nymphaeaceae, Oleaceae, Oxalidaceae, Palmae, Papilionaceae, Pandanaceae, Phytolacaceae, Piperaceae, Plantaginaceae, Polygalaceae, Polypodiaceae, Primulaceae, Punicaceae, Ranunculaceae, Rhamnaceae, Rhizophoraceae, Rosaceae, Rubiaceae, Rutaceae, Salsolaceae, Sapotaceae, Scrophulariaceae, Simarubiacea, Solanaceae, Sterculiaceae, Theaceae, Turneracea, Verbenaceae, Zygophyllaceae, etc [41,42].

Antidiabetic Plants in Clinical trials

Allium cepa L., *Clerodendron phlomoides* Linn., *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm., *Coccinia indica* Wight & Arn., *Enicostemma littorale* Blume, *Ficus bengalensis* L., *Momordica charantia* L., *Pterocarpus marsupium* Roxb., *Cyamopsis tetragonolobus* (L.) Taub., *Cephalandra indica* Naud., *Casearia esculenta* Roxb., *Cannabis indica* (Lam.) E. Small & Cronq., *and Syzygium cumini* L. when subjected to clinical trials, showed promising hypoglycaemic effects [43,44]. *Cecropia obtusifolia* Bertol. and *Marrubium vulgare* L. produced beneficial effects on carbohydrate and lipid metabolisms when it was administered as an adjunct on patients with type 2 diabetes and reduced the blood glucose levels [45]. *Asteracantha longifolia* Nees was reported to improve glucose tolerance in healthy human subjects and diabetic patients. Significant reduction in glycaemia was observed when *Panax quinquefolius L* was taken 40 min before glucose load in non-diabetic subjects and the same result was seen in diabetic subjects. *Gymnema Sylvestre* R. Br. treated patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins. Intake of *Opuntia streptacantha* Lem. by the type II group was followed by a significant reduction in serum glucose and insulin concentration reaching 40.8 mg/dL and 7.8 μU/mL less than basal values at 180 min. Acute hypoglycaemic effect of nopal was observed in patients with type II diabetes but not in healthy subjects. In 10 human subjects, when treated with a preparation of the whole plant, *Phyllanthus amarus* Shum. & Thon. for ten days, the blood glucose level was reduced. The treatment with *Withania somnifera* Dunal produced a decrease in blood glucose levels that was comparable with effects of an oral hypoglycaemic drug [42].

Mechanism of Action of Herbal Antidiabetics

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as-

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation [27]
- Inhibition in renal glucose reabsorption [32]
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes [41]

- Reduction in insulin resistance [41]
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells [42]
- Regenerating and/or repairing pancreatic beta cells [42]
- Increasing the size and number of cells in the islets of Langerhans [42]
- Stimulation of insulin secretion [46]
- Stimulation of glycogenesis and hepatic glycolysis [47]
- Protective effect on the destruction of the beta-cells [48]
- Improvement in digestion along with reduction in blood sugar and urea [49]
- Prevention of pathological conversion of starch to glucose [50]
- Inhibition of β -galactocidase and α–glucocidase [51]
- Cortisol lowering activities [52]
- Inhibition of alpha-amylase [53]
- Preventing oxidative stress that is possibly involved in pancreatic ß-cell dysfunction found in diabetes [54]

Hence, the wide range of plant constituents could have different sites of action within the body, herbs exerts different mechanism of actions including the mechanism of actions of synthetic oral hypoglycemic drugs.

Phytoconstituents with Antidiabetic Activity

The constituents that comes under the category of polysaccharides, peptides, alkaloids, glycopeptides, triterpeniods, amino acids, steroids, xanthone, flavonoids, lipids, phenolics, coumarins, iridoids, alkyl disulphides, inorganic ions and guanidines are reported to have antidiabetic activity [39, 41]. Specifically the following constituents are reported to have antidiabetic activity, aminoacids like hypoglycin A and hypoglycin B, alkaloids like catharanthine, leurosine, lochnerine, arecoline and vindoline, pinitol, epicatechin, bengalenoside, anemarans (A,B,C,D), atractans (A,B,C), dioscoran (A,B,C,D,E,F), ephedrans (A,B,C,D,E), glycoproteins (moran A), mucilage, nimbidin, peptides (P-insulin), S-methyl cysteine sulphoxide, S-allyl cysteine sulphoxide, andrographolide, allicin (thio-2-propene-1-sulfinic acid S-allyl ester), shamimin, beta vulgarosides I–IV, glycoside of leucopelargonidin and leucodelphinidin, mangiferin, marsupsin, pterosupin, pterostilbene, salacinol, swerchirin, trigonelline, berberine, harmane, norharmane, pinoline, quercetin, chlorogenic acid, hesperidin, naringin, epigallocatechin gallate, charantin, galactonmannan, lactucain C, furofuran lignan, lactucaside, beta-sitosterol, gymnemic acid IV, elatosides (E,G,H,I), oleanolic acid, kalopanax saponin A, hederagenin, cryptolepine, Shamimin, chamaemeloside, momordin Ic, scoparianosides A, B and C, trihydroxyoctadecadienoic acids, kaempferol glucosides, caffeoyl glucoside, bakuchiol, swerchirin, thysanolactone, bellidifolin, kolaviron, escins (Ia, Ib, IIa, IIb and IIIa), kotalanol, fagomine, 4-O-beta-D-glucopyranosylfagomine, 3-O-beta-Dglucopyranosylfagomine, 3-epifagomine, myrciacitrins I and II, myrciaphenones A and B, 4-hydroxybenzoic acid, senegin II, Z-senegasaponins a and b, E and Z-senegasaponins, E and Z-senegins (II, III, and IV), paeoniflorin, 8-debenzoylpaeoniflorin, prunin, coutareagin, masoprocol, and oleanolic acid glycosides, ginsenoside, senticoside A, boussingoside, momordin, tormentic acid, ursolic acid, panaxan, laminaran, coixan, pachymaran, lithosperman, trichosan, saciharan, abelmosan, kakonein, flavone C-glycoside, icariin, neomyrtillin, sappanchalcone, caesalpin P, 3-deoxysappanone, protosappanin A, brazilin, hyperin, berberin, anisodamine, multiflorine, 1-deoxynojirimycin, acarbose, voglibose, and ferulic acid [35,41-43,55]. In addition, a major effort was directed toward discovery of novel antidiabetic agents, which resulted in the discovery of several patented compounds: cryptolepine, maprouneacin, 3β,30-dihydroxylupen-20(29)-en-2-one, harunganin, vismin, and quinines SP18904 and SP18905. The most interesting discovery was nordihydroguaiaretic acid (ndga), which, besides being active orally in db/db diabetic mice, also lowered cholesterol levels. This is considered as the unique quality of herbs, which was not observed in any synthetic medicines [26].

Marketed Products

Today, up to 600 traditional plant medicines has been reported in India for diabetes. Numerous medicinal preparations in varied forms have been tried out and are used in Ayurvedic system of medicines for diabetes. These medicines are prescribed in different forms; most commonly used are - choorna, vati, arka, quath, etc. These preparations may contain the aqueous extracts or powders of the different parts of the plants which are used in the treatment of diabetes. All the antidiabetic formulations available in the market contain 3 to 25 herbs and mainly, used herbs are Coccinia indica, Tragia involucrata, G. sylvestre, Pterocarpus marsupium, T. foenum-graecum, Moringa oleifera, Eugenia jambolana, Tinospora cordifolia, Swertia chirayita, Momordica charantia, Ficus glomerata, Ficus benghalensis, Vinca rosea, Mucuna prurita, Terminalia bellirica, Azadirachta indica, Zingiber officinale, Aegle marmelos, Cinnamomum tamala, Ocimum sanctum, Salacia oblonga, Cassia auriculata, Curcuma longa, Andrograpis paniculata, Emblica officinalis, etc. Following are few preparations available in the market for the treatment of diabetes that contains drug in powder form or as extracts. Only the names of the herbs added in the preparations are reported, along with these herbs some preparations may contain animal-derived products and minerals.

Hyponidd tablets, *Momordica charantia*, *Swertia chirata*, *Melia azadiracta*, *Tinospora cordifolia*, *Gymnema sylvestre*, *Enicostemma litterole*, *Emblica officinalis*, *Eugenia jambolana*, *Cassia auriculata*, *Curcuma longa*.

Mersina capsules, *Gymnema sylvestre*, *Momordica charantia*, *Cassia auriculata*, *Syzigium cumini*,

Phyllanthus emblica, *Melia azadiracta*, *Trigonella foenum graecum*, *Coccinia indica*, *Tinospora cardifolia*, *Potassi carbonas*.

Herbovedics mahantak churna, Nai, Kadu, Kariyatu, Kalijeeri, Methi, Kalumbo, Kakach, Indrajav, Karela, Haldi, Jeshthimadha.

Madhuhari powder, Gudmar, Karela beej, Jamun, Babul ki chhal, Amba haldi, Gudwel, Bilva patra, Neem patra, Shilajeet, Trivang bhasm.

Dianex, *Gymnema sylvestre*, *Eugenia jambolana*, *Momordica charantia*, *Azadirachta indica*, *Cassia auriculata*, *Aegle marmelos*, *Withania somnifera* and *Curcuma longa*.

Diamed, *Azadirachta indica*, *Cassia auriculata* and *Momordica charantia*.

Aavirai kudineer, *Cassia auriculata*, *Cassia fistula*, *Salacia prinoides*, *Cyperus rotundus*, *Saussurrea lappa*, *Eugenia jambolana* and *Terminalia arjuna*.

Madhumeha churna, *Azadirachta indica*, *Cassia auriculata*, *Cassia auriculata*, *Gymnema sylvestre*, *Eugenia jambolana*, *Eugenia jambolana*, *Zizyphus mauritiana*, *Curculigo orchioides*, *Melochia corchorifolia*, *Michelia champaca*, *Cynodon dactylon*, *Murraya koenegii*, *Acacia catechu*, *Cassia fistula*, *Salacia oblonga* and *Momordica charantia*.

Diagon tablets, *Eugenia jambolana*, *Andrograpis paniculata*, *Tinospora cordifolia*, *Curcuma longa*, *Berberis aristata*, *Vetiveria zizanoides*, *Strychnos potatorum*, *Mimosa pudica*, *Gymnema sylvestre*.

Glucolev capsule, Amalaki powder, Sudha shilajeet, Jasad bhasma, Methika beej, Jambu beej, Madhunasini, Ashwagandha

Gluco-essentials capsules, *Vaccinium myrtillus*, *Gymnema sylvestris*, *Momordica charantia*, *Cinnamomum zeylanicum*, *Trigonella foenum graecum*, *Panax quinque*, *Panax ginseng*, *Viscum alba*, *Amorphophallus konjac*, *Hydrastis cadensis*, *Ocimum basilicum*, *Cynara scolymus*, *Plantago ovata*, *Pfaffia paniculata*, *Arctostaphylos uva ursi*.

Diasulin, *Casssia auriculata*, *Coccinia indica*, *Curcuma longa*, *Momordica charantia*, *Scoparia dulcis*, *Gymnema sylvestre*, *Emblica officinalis*, *Syzgium cumini*, *Tinospora cordifolia*, *Trigonella foenum graecum*.

Glucolib, *Eugenia jambolana*, *Gymnema sylvestris*, *Aegle marmelos*, *Melia azadiracta*, *Momordica charantia*, *Enicostema littorale*, *Trigonella foenum graecum*.

Diaveda capsule, *Trigonella foenum graecum*, *Emblica officinalis*, *Curcuma longa*, *Melia azadiracta*, *Gymnema sylvestris*, *Tribulus terrestris*, *Tinospora cordifolia*, *Syzygium cumuni*, *Azadirachta indica*, *Terminalia belerica*, *Terminalia chebula*, *Piper nigrum*, *Piper longum*, *Zingiber offcinalis*.

GlucoCare, *Glycyrrhiza glabra*, *Asparagus racemosus*, *Pterocarpus marsupium*, *Gymnema sylvestris*, *Momordica charantia*, *Commiphora mukul*.

Glucomap tablets, *Enicostema littorale*, *Phyllanthus niruri*, *Eugenia jambolana*, *Melia azadiracta*, *Terminalia arjuna*, *Asphaltum*, *Aegle mermelos*, *Momordica charantia*.

Glucova, *Pterocarpus marsupium*, *Enicostema littorale*, *Eugenia jambolana*, *Tinospora cordifolia*.

Pancreas tonic, *Tinospora cordifolia*, *Sygigium cumini*, *Melia azadiracta*, *Momordica charantia*, *Gymnema sylvestra*, *Pterocarpus marsupium*, *Aegle mermelos*, *Cinnamomum zeylanicum*.

Tincture of Panchparna, *Coccinia indica*, *Cocculus villosus*, *Catharanthus roseus*, *Gymnema sylvestre* and *Momordica charantia*.

DWN-12, *Strychnos potatorum*, *Terminalia chebula*, *Emblica officinalis*, *Terminalia belerica*, *Salacia reticulata*, *Pterocarpus marsupium*, *Piper longum*, *Coscinium fenestratum*, *Tribulus terrestris*, *Syzigium cumini*, *Rhabdia lyuoides*, *Elettaria cardamomum*.

CONCLUSION

Herbal therapy for diabetes has been followed all over the World successfully. Herbs are used to manage Type 1 and Type II diabetes and their complications. The above-mentioned plants have been considered for their possible hypoglycaemic actions and the researchers have carried out some preliminary investigations. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level. However, there are numerous other plants still await scientific inquiry, which have mentioned in the indigenous systems of health care all over the world. A large number of plants, screened for their antidiabeiic effect, have yielded certain interesting leads as mentioned above, but till to date no plant-based drug has reached such an advanced stage of investigation or development as to substitute or reduce the need for the currently-available oral synthetic drugs. However, the interest in herbal drug research continues with an expectation that some day or the other, we would be able to bring a safer and more effective compound with all the desired parameters of a drug, that could replace the synthetic medicines.

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