

Herbal Drugs for Diabetic Treatment: An Updated Review of Patents

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Received: June 11, 2011; Accepted: October 18, 2011; Revised: January 10, 2012

Abstract: Diabetes mellitus is the most common endocrine disorder, affecting 16 million individuals in the United States and 200 million worldwide. Despite the use of advanced synthetic drugs for the treatment, use of herbal remedies is gaining higher importance because of synthetic drugs have drawbacks and limitations. The herbal drugs with antidiabetic activity are extensively formulated commercially because of easy availability, affordability and less side effects as compared to the synthetic antidiabetic drugs. Antidiabetic herbal formulations (AHF) are considered to be more effective for the management of diabetes. There are around 600 herbal drug manufacturers in India of which almost all manufacturers are developing AHF in addition to others. Till date, no article is published to give detailed information of the patents on AHF. Thus, this review article undertake the attempt for providing updated information on the type of diabetes and patented AHF which will enhance the existing knowledge of the researchers.

Keywords: Anti-diabetic herbals, diabetes, nutraceuticals, Phytopharmaceutical agents.

INTRODUCTION

WHO defined Diabetes mellitus as “a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both” [1]. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs including kidney, nerves, heart and gastrointestinal tract. It is the most common endocrine disorder world-wide with an incidence varying between 1 to 8% [2]. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025 [3]. Diabetes is classified into two major categories i.e., insulin dependent diabetes (Type-1) and non-insulin dependent diabetes (Type-2 diabetes). Despite the advancement in the synthetic anti-diabetic drugs in the recent past, diabetes is still remarkably not cured successfully. Treatment of diabetes is complicated due to the lack of drugs with safety and efficacy, and are incapable of sustained clinical, biochemical, and histological cure. On the contrary the herbal drugs have gained wider importance worldwide, mostly due to higher safety, less number of adverse effects and consistent blood glucose lowering capacity. In the developed countries, the use of herbal medicine for the sufferers of diabetes is encouraged by the concern about the adverse effects and cost associated with chronic use of synthetic drug. There are wide range of phytoconstituents useful in the treatment of diabetes. These include alkaloids,

glycosides, peptidoglycan, hypoglycan, steroids, guanidine, glycopeptides, terpenoides, amino acids and inorganic ions. According to ethno botanical survey, there are about 800 plants which possesses antidiabetic potential [4]. Among the type-2 diabetic patients, 25% uses herbal drugs, while 75% still rely on synthetic modern drugs. However, 10% of type-1 diabetic patients frequently use medicinal plants, in addition to insulin treatment [5].

Antidiabetic herbal formulations (AHF) are considered to be more effective for the management of diabetes [6] as compared to single herbs. There are around 6000 herbal drug manufacturers in India. Till date, no article is published to give detailed information on the patented AHF. The present review gives an exhaustive account to update on the several types of diabetes and patented AHF to upgrade the existing knowledge on the prior art.

DIABETES AND ITS TYPES

Classification of diabetes into type-1 or 2 based on the clinical presentation may be difficult [7]. Diagnosis of the main forms of diabetes depends on clinical judgment based mainly on the age of the subject and the severity of insulin deficiency at presentation, as well as the presence or absence of features of the metabolic syndrome [8]. As per WHO classification in 1998, an etiological classification was chosen to subgroup diabetes mellitus into different types. [9]

TYPE-1 DIABETES MELLITUS

Insulin-dependent diabetes (IDDM; Type I diabetes) is one of the most serious metabolic disorders, affecting approximately 1 person in 300 in the U.S., while epidemiological studies in Europe suggested that the incidence are in-

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creasing [10, 11]. Type-1 diabetes occurs due to permanent (95%) destructions of β -cells of islets of Langerhans present in the pancreas, by an autoimmune process, or other unknown causes leading to absolute insulin deficiency. An individual with Type-1 process may be metabolically normal before the disease is clinically manifest, but the process of β -cell destruction can be detected. On the basis of etiology it is further classified as Immune Mediated and Idiopathic one.

IMMUNE MEDIATED DIABETES

This form of diabetes is the results of a cell-mediated autoimmune destruction of the β -cells in the pancreas. It is characterized by the presence of Anti-glutamic acid decarboxylase (Anti-GAD) antibodies, islet cell or insulin antibodies without processes that lead to β -cell destruction [12]. Thus, this category of type-1 diabetes can be identified if appropriate antibody determinations are performed [13]. Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia or ketoacidosis in the presence of infection or other stress. Still others, particularly adults may retain residual β -cell functions sufficient to prevent ketoacidosis for many years. Many such individuals with this form of type-1 diabetes eventually require insulin for survival.

IDIOPATHIC DIABETES

In some subjects with type-1 diabetes, particularly non-Caucasians, no evidence of an autoimmune disorder is demonstrable and these are classified as idiopathic type-1. Only a minority of patients with type-1 diabetes fall into this category and showed clinical symptom of episodic ketoacidosis with varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited and it is not associated with HLA.

TYPE-2 DIABETES MELLITUS

The most common type of diabetes mellitus constituting about 90% of diabetic population and often associated with a family history of diabetes, older age, obesity and lack of exercise [14]. It is characterized by disorders of insulin action and insulin secretion, either of the two which may be the predominant feature. Both are usually present at the time when this form of diabetes is clinically manifested. The specific reasons for the development of these abnormalities are not yet known [13]. Ketoacidosis is very rare in type 2 diabetes and does not require insulin therapy. The insulin resistance occurs in this type is partly explained by the obesity that often coexists with the disease.

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes is a state of carbohydrate intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may lead to pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy

[1]. Women who are known to have diabetes mellitus and who subsequently become pregnant do not have gestational diabetes but have "diabetes mellitus and pregnancy" and should be treated accordingly before, during and after the pregnancy. In the early part of pregnancy (e.g. first trimester and half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal, non-pregnant women. Elevated fasting or postprandial plasma glucose levels may well reflect the presence of diabetes that antedates pregnancy, but criteria for designating abnormally high glucose concentration at this time in pregnancy have not yet been established. The occurrence of higher than usual plasma glucose levels at this time in pregnancy mandates careful management and may be an indication for carrying out an OGTT.

OTHER SPECIFIC TYPE OF DIABETES

Many other form of diabetes are associated with monogenetic defects in β -cell function and characterized by onset of hyperglycemia at an early age called as maturity-onset diabetes of the young (MODY) further, it also showed impaired insulin secretion with minimal or no defects in insulin action. [15-17]

Other specific types are currently less common causes of diabetes mellitus, but the conditions in which the underlying defect or disease process can be identified in a relatively specific manner, this include

- Genetic defects in insulin action, such as leprechaunism
- Diseases of the exocrine pancreas, such as cancer of the pancreas, cystic fibrosis and fibrocalculous pancreatopathy (a form of diabetes, which was formerly classified as one type of malnutrition-related diabetes mellitus)
- Endocrinopathies, such as cushing syndrome, acromegaly and pheochromocytoma
- Drugs or chemicals, such as steroids and thiazides
- Infections, such as rubella
- Uncommon forms of immune-related diabetes, such as the type associated with as Klinefelter
- Other rare genetic syndromes associated with diabetes, such as Down syndrome.

PHYTOCONSTITUENTS IN THE TREATMENT OF DIABETES MELLITUS

Many phytoconstituents isolated from plants including the compounds belongs to the class of alkaloids, glycosides, terpenoids, flavonoids are constituted as vital elements to combat diabetes mellitus. However, the use of single phytoconstituents in the treatment of diabetes is quite ineffective. Examples of some of the important phytoconstituents are described in the prior art of patent literatures. These includes traditional Indian medicinal plants and modern herbs like *Gymnema sylvestre*, *Momordica charantia*, *Syzygium cumini*, *Pterocarpus marsupium*, *Trigonella foenum-graceum*, *Cinnamomum tamala*, *Withania somnifera*, *Coccinia indica*, *Pueraria tuberosa*, *Asparagus racemosus*, *Boerhaavia diffusa*, *Aegel marmelos*, *Piper longum*, *Chlorophytum tuberosum*, *Curcuma longa*, *Lagerstroemia speciosa* and *Elettaria*

Table 1. Patented Instances on Recently Explored Anti-diabetic Herbal Formulations for the Treatment of Diabetes

Summary of Invention	Patent Number	Inventor/Assignee	References
Anti-diabetic and cholesterol lowering preparation from fenugreek seeds	US7815946	Murthy, P.S., Moorthy, R., Prabhu, K.M., Puri, D.	[18]
Synergistic composition for the treatment of diabetes mellitus	US7641925	Bhaskaran, S., Mohan, V	[19]
Pharmaceutically active extracts of vitex leucoxyton, a process of extracting the same and a method of treating diabetes and inflammatory diseases therewith	US7780997	Raju, G.G., <i>et al</i>	[20]
Synergistic composition for the treatment of diabetes mellitus	US7736676	Bhaskaran, S., Mohan, V.	[21]
Methods of using pomegranate extracts for treating diabetes related atherosclerotic complications in humans	US7727563	Aviram, M.	[22]
Synergistic composition for the treatment of diabetes mellitus	US7674486	Bhaskaran, S., Mohan, V	[23]
Method of treating non-insulin dependent diabetes mellitus and related complications	US20100292178	Young, J.	[24]
Novel anti-diabetic herbal composition, method for preparing the same and use thereof"	US20090238900	Mitra, S.K., Saxena, E., Babu, U.V.	[25]
Methods for the treatment or prevention of Diabetes Mellitus and other metabolic imbalances"	US20090252817	Hayes, K.C., Sundram, K., Sambanthamurthi, R., Tan, Y.A.	[26]
Anti- diabetes extract isolated from Rauvolfia vomitoria and Citrus aurantium, and methods of using same	US20090041873	Campbell-tofte, J.	[27]
Natural herb composition for the treatment of diabetes-sand manufacturing method	US7482030	Mansilla, A.	[28]
Berry preparations for treatment of diabetes and metabolic syndrome	US20090176718	Ribnicky, D., Raskin, I.	[29]
Anti-diabetics extract isolated from Rauvolfia vomitoria and Citrus aurantium, and methods of using same	US7579025	Campbell-tofte, J.	[30]
Extracts, compounds and pharmaceutical compositions having anti-diabetic activity and their use	US7416744	Rubin, I.D., Bindra, J.S., Cawthorne, M.A.	[31]
Natural herb composition for the treatment of diabetes and manufacturing method	US20080299236	Mansilla, A.	[32]
Herbal product to be administered to diabetic people and process	US20080206372	Agreda, N.J., Martin, P.F., Belo, M.E.W.	[33]
Anti-diabetics extract isolated from Rauvolfia vomitoria and Citrus aurantium, and method of using same	US7429395	Campbell-tofte, J.	[34]
Pharmaceutically active extracts of Vitex leucoxyton, a process of extracting the same and a method of treating diabetes and inflammatory diseases	US20080199543	Gokaraju, G.R., Gokaraju, R.R., Gottumukala, V.S., Somepalli, V.	[35]
Herbal extract and compound lupinoside and its analogues as anti-diabetic type-2drugs from plant Pueraria tuberosa	US7276258	Dey, D., <i>et al</i>	[36]

(Table 1) Contd....

Summary of Invention	Patent Number	Inventor/Assignee	References
Herbal nutraceutical formulation for diabetics and process for preparing the same	US7014872	Pushpangadan, P., Prakash, D.	[37]
Synergistic composition for the treatment of diabetes mellitus	US7141254	Bhaskaran, S., Mohan, V.	[38]
Herbal nutraceutical formulation for diabetics and process for preparing the same	US20060147561	Pushpangadan, P., Prakash, D.	[39]
Process and product extracted from herbal composition useful in controlling diabetes mellitus type-2	US7056539	Leko, V.	[40]
Extracts, compounds and pharmaceutical compositions having anti-diabetic activity and their use	US7033616	Rubin, I.D., Bindra, J.S., Cawthorne, M.A.	[41]
Method of treating diabetes type-2	US20060177530	Crea, R.	[42]
Synergistic composition for the treatment of diabetes mellitus	US20060153937	Bhaskaran, S., Mohan, V.	[43]
Anti-diabetics extract isolated from Rauwolfia vomitoria and Citrus aurantium, and method of using same	US20060115543	Campbell-tofte, J.	[44]
Synergistic composition for the treatment of diabetes mellitus.	US20060134242	Bhaskaran, S., Mohan, V.	[45]
Herbal formulation	US7125571	Organ, E.J., Organ, D.L	[46]
Compositions for diabetes treatment and prophylaxis	US6949261	Chatterji, A.K.	[47]
Herbal extract and compound lupinose and its analogues as Anti-diabetics type-2 drugs from plant pueraria tuberosa	US20050153000	Dey, D., et al.	[48]
Method for treating type-2 diabetes with an extract of Artemisia	US6893627	Ribnicky, D.M., Raskin, I.	[49]
Herb extract-based cosmeceutical cream for controlling the blood sugar level of diabetes and methods for making it	US20050048144	Han, X., Liu, M.	[50]
Good living tea - a diabetic dietary supplement drink	US20050118324	Mathew, A.M., Mathew, T.M.	[51]
Herbal product to be administered to diabetic individuals and the production method thereof	EP1502596	Belomalendas, E.W.	[52]
Dietary supplement for promoting control of blood sugar levels and associated pathology in type-2 diabetics	WO2005009351	Arthur, D.	[53]
Antidiabetic dietetic nutritional supplement, effective against type-1 and type-2 diabetes, comprises processed material from hibiscus plants, especially okra	DE202004017554	Doku, A., Gazmend, M.	[54]
Herbal compositions and methods for diabetes and weight loss management	US6780440	Naguib, Y.M.A.	[55]
Pharmaceutical composition for the treatment of diabetes mellitus	US6692777	Lee, S.Y.	[56]
Method for extraction and separation of vegetable anti-diabetic component	JP2004115421	Fukuoka, H., Miki, K.	[57]
Medicinal herbal compounds for the prevention and treatment of diabetes	US6770307	Yoon, J., Jun, H.	[58]

(Table 1) Contd....

Summary of Invention	Patent Number	Inventor/Assignee	References
Herbal compositions and methods for diabetes and weight loss management	US20030143291	Naguib, Y.M.A.	[59]
Herbal health protective and promotive nutraceutical formulation for diabetics and process for preparing the same	US20030185913	Pushpangadan, P., Prakash, D.	[60]
Process and product extracted from herbal composition useful in controlling diabetes mellitus type-2	US20030206976	Leko, V.	[61]
Herbal composition and medicament against diabetes mellitus type-2 manufactured thereof	US6576270	Leko, V.	[62]
Antidiabetic agent and diet agent	JP2003012529	Yamahara, J.	[63]
Herbal composition and medicament against diabetes mellitus type-2 manufactured thereof	US20020102315	Leko, V.	[64]
Pharmaceutical composition for the treatment of diabetes mellitus	US20020197334	Seung, Y.L.	[65]
Novel herbal composition for diabetes patients and a process for producing the same	US20020025349	Chandrakant, K., Yadlapalli, R., Narasimha, B.	[66]
Herbal composition for diabetes and method of treatment	US 6042834	Baraka, M.W.	[67]
Sugar imbalance and diabetes treating herbal formulation	US6093403	Huo, Y.S., Lo, S.J., Winters, W.D.	[68]
Herbal anti-diabetic therapeutic product containing powdered <i>Dolichos biflorus</i> seeds	US5916567	Kameswaran, N.	[69]

cardamomum have been satisfactorily explored for their anti-diabetic activity. Several mechanisms are proposed for explaining the anti-diabetic activity of these phytoconstituents including GLP-4 inhibitor, DPP-4 inhibitors, stimulation of glucose metabolism through peripheral gluconeogenesis, and sequestration of Ca^{2+} ions from the membrane of the β -cells [18, 19]. An account on several patented literature instances on various types of anti-diabetic herbal formulations are depicted in the Table 1 [18-69].

ANTI-DIABETIC HERBAL FORMULATIONS (AHF) WITH MULTIPLE PHYTOCONSTITUENTS

Instead of using single phytoconstituents for the treatment of diabetes, the herbal formulations containing multiple phytoconstituents are found to be more effective under several clinical studies for reducing blood glucose level. The several compositions of AHF are mentioned provides variable pharmacological action for treatment of diabetes [70]. The multiple combinations of phytoconstituents provide synergistic action. In a US patent 7014872, Pushpangadan and Prakash described AHF containing *Piper longum* fruit powder, *Curcuma longa* rhizome powder, *Chlorophytum tuberosum* and *Elettaria cardamomum* [71].

ANTI-DIABETIC NUTRACEUTICAL FORMULATIONS (ANF)

These include formulations containing a mixture of herbal extracts, constituents from animal and mineral origin

to provide synergistic anti-diabetic action. In a US Patent 7153528, Malleshi *et al.* (2006) described nutraceutical formulation containing soy, fenugreek seed powder, cereals, milk, edible oil, mineral premix, Spice mix, *Garcinia cambogia* etc with enhanced blood glucose lowering action against Type-2 diabetes [72]. Similarly, Massoud described in a European patent about the anti-diabetic herbal formulation containing *Centaurii herba*, *Teraxaci radix*, *Urticac herba*, *Cichorii radix*, *Morus nigra* [73].

MARKETED ANTI-DIABETIC HERBAL PREPARATIONS

Several anti-herbal formulations are currently being marketed in India and Internationally are represented in Table 2.

CONCLUSION

At present the prevalence of Diabetes mellitus has reached 16 million individuals in the United States and 200 million worldwide. Despite of the advancement in drug discovery to synthesize drug, use of herbal remedies are continue because of the existing synthetic drugs have several limitations and side effects. The easy availability, affordability and fewer side effects of herbal drugs with antidiabetic activity are extensively formulated commercially compared to the synthetic drugs. The researches for the herbal drugs are still in the infancy. One can look at the future of integrated medicine and hope that research in alternative medi-

Table 2.

AHF Marketed in India	AHF Marketed Internationally
- Cogent-db capsules	- Pancrease formula
- Diabyog capsules	- Eleotin, Ayubes
- Diabyog capsules	- Diabetes Hypoglycose Capsules
- Diabecon	- Pearl Hypoglycemic Capsules
- Madhu Maheri granules	- Tongyitang Diabetes Angle Hypoglycemic Capsules
- Madhu Sunya	- Zhen-Qi Capsules
- Madhumeh Amrit	

cine will help identify what is safe and effective rather than marginalizing, unorthodox medical claims and findings. The use of traditional/lay remedies in the sample, far from indicating fatalism or non-compliance with modern medicine. Illustrates an effort on the part of the patient to co-opt therapies that are considered efficacious in maintaining good health. Hence, the use of local therapies and their effectiveness warrants further examination.

CURRENT & FUTURE DEVELOPMENTS

Despite of the several anti-diabetic herbal and nutraceuticals formulations for diabetes treatment, the research has taken a drag towards preparing anti-diabetic herbal formulations using novel drug delivery systems for effective treatment of diabetes mellitus. Looking into the score of patent and literature it has been conceived that the area of anti-diabetic treatment by herbal drugs is exploring successfully at a greater pace. This leads to many of the herbal formulation being marketed domestically as well as internationally.

CONFLICT OF INTEREST

Authors have no conflict of interest.

ACKNOWLEDGEMENTS

Authors are thankful to electronic library facility of Jamia Hamdard, New Delhi for preparing the content of the manuscript.

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