IS IT POSSIBLE TO CURE DIABETES MELLITUS BY HERBAL TREATMENT IN TWENTY FIRST CENTURY?

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ABSTRACT

The diabetes is the third leading cause of death in the world. The diabetic population is increasing day by day. The report of WHO shows that the diabetic population was 60 millions in 1980, 118 millions in 1995 and there will be 220 millions in 2010. Therefore, it is very important to focus on the research to find the cure to such disease, which is not only killing the lives and deteriorating the health but also, a huge social and economical burden to the nation.

Although some people prefer to say that diabetes is a Western disease, there is already description of diabetes in the oriental literature claimed as 3500 years old. It is one of the oldest known human diseases. So far known, there are more than 1200 hypoglycemic plants already reported and many of them are used for the treatment of diabetes in several countries. None of the phytomedicines, so far reported, sufficiently meets the criteria for a medicine such as safety, efficacy, mode of action, bioavialibity, dosage, carrier system etc. to be used clinically.

There are several scientific evidences for the cause of diabetes mellitus and one major cause is the gradual destruction of insulin-producing β-cells in the pancreas. On this regard, the role of GAD-65, IRS, Th1 and Th2 cells activities, and reactive oxygen spices (ROS) including SOD-activity, have been studied. Vitamin C, vitamin E, nicotinamide, lipoic acid, N-acetyl-L-cysteine are some of the substances showing the preventive action on diabetes. However, there is no systematic study on the role of natural medicines and their actions in preventing diabetes.

The main challenge for the natural medicines in 21st century is the systematic study. In the present review, an attempt was made to focus on the medicinal plants which are used as a traditional medicine in more than two countries. Moreover, only a few of them are taken to clinical trails. The total literature survey suggests that the use of hypoglycemic plant remedies clinically requires further systematic study.

INTRODUCTION

Diabetes mellitus (DM) is regarded as one of the oldest known diseases in human societies. The symptoms of diabetes such as polyurea, polyphagea, excessive thrust, weakness, losing weight etc., had already been well illustrated in Chinese or Indian ancient literature dated back 3500 years (Hengesh and Holcomb, 1981). The treatment for DM such as exercise, controlled food habit and some herbal remedies had already been practiced. In spite of all this, DM is often wrongly referred as a Western disease. In fact, DM is the disease related to metabolic disorder, therefore, the food habit and living style are the main cause of DM. In an attempt of evidence-based medicine, an epoch-making discovery in 1921, that a pancreatic extract (insulin) would lessen the symptoms of diabetes, was a landmark in the area of antidiabetic drugs from natural sources. At the time of insulin discovery, it was hoped that it would be a cure for DM. People were disappointed since it took more than 10 years to understand the proper dose of insulin and it was not the actual cure for DM, but way to control the glycemia. However, the treatment of insulin was life saving and prolonged the life of those people who have to die early because of ketoacidosis or diabetic complications.

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is widely available, more deaths are attributed to diabetes than to cancers or motor vehicle accidents (World Health Organization, 1985). It has been considered that DM is the third leading cause of human death in the world. The report of WHO shows that the population of diabetics was 60 millions in 1980, 118 millions in 1995 and there will be 220 millions in 2020 (Amos et al, 1997). Every year diabetic population is increasing in spite of all research and education in this area. More than 10% Japanese population of over 40 years is suffering from type II diabetes (NIDDM: Non Insulin Dependent Diabetes Mellitus, i.e. insulin is insufficiently produced or hyperinsulinema or insulin does not function properly, however external insulin is not required). Although the number of Type I diabetes (IDDM: Insulin Dependent Diabetes Mellitus, i.e. insulin can not be produced within the body, therefore external insulin is required) population is very low comparing to Western countries, more than 6000 people are suffering from such incurable disease in Japan. Therefore, it is very important to focus on the research aim to find cure for such disease which is not only killing the lives, but deteriorating health and also a huge social economic burden to the nation. Only in USA, direct medical costs due to diabetes are estimated to have been 9.6 billion US$, and indirect costs for short term morbidity, long-term disability, and mortality are estimated to have been 10 billion US$ (Center for Economic Studies in Medicine 1988). The enormous costs of modern treatment indicate that alternative strategies for the prevention and treatment of diabetes must be developed. Moreover, almost 90% of the people in rural areas of developing countries still rely on traditional medicines for their primary health care. A synthesis of traditional and modern knowledge may lead to effective and cost-efficient alternatives.

Whether it is Type I or II, the main cause of diabetes is the loss of β-cells either due to toxic chemicals from external environment, viral infection or diet. In addition to this, immunological factors such as autoimmune disorders have been considered as the focus for the cause of Type I to genetically vulnerable individuals (Unger and Foster, 1985). Type II diabetes is generally found in older population and often associated with obesity. More than 15% of people over 65 years of age have Type II (Ilarde and Tuck, 1994). In Type II, either insulin is excessively produced with its improper function or production of insulin is not sufficient. In both conditions, the patients suffer with an elevated blood glucose level causing the metabolic disorder.

Before the modern therapy, herbal treatment, diet and exercise were the way of treatment for the DM patients. Such method still exist as a part of treatment but this treatment is not beneficial to the Type I diabetes, although it is often beneficial for the several cases of Type II diabetes. The focus on pancreas has been started since 1889 after von Mering and Minkowski who found that pancreas has a great role to control glycemia. The successful experiment was carried out by Banting and Best in 1921 for the use of pancreatic extract, what we call insulin today, to reduce the elevated blood glucose level, which has been considered as the foundation of modern treatment for the diabetic people. Insulin controls the absorption of glucose in the intestine, reverses the neoglucogenesis process, activates the hepatic enzymes, activates and generates the glucose transporter in the fibroblasts, suppresses the function of glucagon and other hormones, activates the glycogenesis and fat synthesis. All these actions of insulin help to lower the elevated glucose level to normal. Therefore, the major concern for the research on diabetes remained mainly to be the action mechanism of insulin after its discovery since 1921. Insulin plays a vital role to control the glycemia, however, it could not be the total solution to overcome the diabetes. Moreover, insulin being a polypeptide (51 aminoacids), the oral route of administration is not effective, since it is digested in the intestine. In addition to this, it has shorter life span in the human body, therefore, its effect is not long lasting. On the other hand, the daily pain of using insulin and its difficulty of handling for DM patient

encouraged the scientists to discover oral hypoglycemic agents. In the mean time, during World War II when insulin was not available in many of the countries, search was made for an insulin substitute from plant sources. Soon after the World War II, oral hypoglycemic agents were made available for the clinical use that exceeds more than 88 types up to now (Soejarto and Farnsworth 1989).

WHY MEDICINAL PLANTS ARE SO IMPORTANT?

Discovery of insulin together with 88 clinically used oral hypoglycemic drugs did not solve the problem of diabetes. Many of the oral hypoglycemic drugs are not effective when they are used for long time. Because of this reason, people are still hoping to find a solution for diabetes in natural medicine. Several attempts were made to discover the effect of the natural medicine, especially to potentiate the β-cells for the production of more insulin. Most of the natural medicines were studies for their hypoglycemic effect in normal or diabetic animal models. Based on the pharmacological tests, more than 1200 medicinal plants were reported for their alleged hypoglycemic effect, however the action mechanism may be different. Many of the medicinal plants are used traditionally as the antidiabetic remedy in different cultures. There are still more researches going on to find more antidiabetic plants. However, no medicinal plants can be considered up to now as the evidence based medicine in spite of huge efforts of scientists all over the world, as it is hoped that herbal remedy will be a solution for the treatment of diabetes in the future. Researchers may have individual interest and it should not be limited. However, it should be the matter of interest to know why the people in three or more different cultures are using same medicinal herb for the same purpose. For this reason, ethnomedicines are of great importance. Despite the difficulties, the financial rewards of success in marketing plant-derived drugs are great. In many developed countries 25% of all prescriptions dispensed from community pharmacies contained active principles prepared from plants. Of the 121 natural products currently in pharmaceutical use, only 12% are produced commercially by synthesis (Fransworth et al., 1985). Therefore, the medicinal plants are of great value. Several medicinal plants yet have to be tested for their antidiabetic activity. Therefore, it can be hoped that the herbal treatment for the diabetic people would be economically and therapeutically useful. For this aim, the plants falling under following general criteria could be useful:

1. Same medicinal herb using in different ethnic culture for the antidiabetic purpose
2. Experimentally known antidiabetic activity in several animal models and clinical trial
3. Nontoxic within the range of effective dose
4. High botanical abundance

Table 1: Antidiabetic Plants Used as Ethnomedicines in More than Two Countries

Family	Scientific name	ETM	Part tested	Route	Toxicity	Active constituents
Alismataceae	*Alisma orientale*	3	rz	po,sc	N	—
Anacardiaceae	*Anacardium occidentale*	9	lf,sb,sd	po,iv	T	(-)-epicatechin
Apiaceae	*Coriandrum sativum*	3	sd	po	N	diphenylamine
Apiaceae	*Daucus carota*	4	rt,wp	po,sc	?	—
Apocynaceae	*Catharanthus roseus*	10	lf	po	T	catharanthine, lochnerine, tetrahydroalstonine, leurosine sulphate vindoline, vindolidine
Araceae	*Pistia stratiotes*	3	—	—	T	—
Asteraceae	*Arctium lappa*	4	rt	sc	N	—
Asteraceae	*Centaurea melitensis*	3	fl	po	N	—
Asteraceae	*Neurolaena lobata*	3	lf	po	T	—
Asteraceae	*Taraxacum officinale*	4	wp	po	N	—
Brassicaceae	*Nasturtium officinale*	3	—	—	N	—

Family	Scientific name	ETM	Part tested	Route	Toxicity	Active constituents
Cactaceae	*Opuntia ficus-indica*	3	wp	po	?	pectin
Cornaceae	*Cornus officinalis*	3	fr	po	N	ursolic acid, oleanolic acid
Cucurbitaceae	*Citrullus colocynthis*	3	wp	po	T/N	–
Cucurbitaceae	*Coccinia indica*	3	fr,lf,st,rt	po	N	quaternary alkaloid
Cucurbitaceae	*Momordica charantia*	12	fr, sd	po,sc,iv	T/N	polypeptide p, charantin:daucosterol, (+)-5,25-stigmastadien-3 β-ol-glucoside
Cyperaceae	*Kyllinga monocephala*	4	–	–	–	–
Dioscoreaceae	*Dioscorea batatas*	3	rz	ip,po	N	dioscorans a-f
Euphorbiaceae	*Phyllanthus emblica*	4	sd	po	T	–
Euphorbiaceae	*Phyllanthus niruri*	4	lf	po	T	lupeol lupeol acetate
Fabaceae	*Acacia nilotica*	3	sd,gm	po	N	–
Fabaceae	*Lupinus albus*	5	sd,wp	po	T	lupanine, sparteine
Fabaceae	*Lupinus termis*	3	sd	po,sc	T	lupanine, coumarin, sparteine
Fabaceae	*Trigonella foenum-graecum*	4	sd,wp	po	N	trigonelline,coumarin nicotinic acid nicotinamide fenugreekine
Fabaceae	*Vicia faba*	3	–	–	N	–
Fumariaceae	*Fumaria parviflora*	3	ap	po	?	–
Juglandaceae	*Juglans regia*	3	lf	sc	N	–
Lamiaceae	*Ajuga iva*	3	–	–	N	–
Lamiaceae	*Orthosiphon grandiflorus*	3	lf	po	?	ursolic acid
Lauraceae	*Persea Americana*	3	–	–	N	–
Liliaceae	*Allium cepa*	4	ap,bl	po,sc,ip,iv	N	allylpropyl disulphide, allicin, diphenylamine
Liliaceae	*Allium sativum*	5	bl	po	N	allylpropyl disulphide, allicin
Liliaceae	*Aloe vera*	5	lf	po,iv,ip	?	Lupol
Liliaceae	*Anemarrhena asphodeloides*	3	rz	po, ip	N	anemarans a-d
Meliaceae	*Azadirachta indica*	4	lf,sd	po,iv	N	nimbidin, daucosterol, flavonol glycosides
Moraceae	*Ficus religiosa*	3	rb,rt	po	N	daucosterol
Moraceae	*Morus alba*	4	lf,rb	po,sc,ip	N	phytosterol glycoside scopoletin, moran a, glycoproyein, moranoline
Myrtaceae	*Eucalyptus globulus*	5	lf	po,ip	N	calyptoside
Myrtaceae	*Syzygium cumini*	6	ap,sd	po	N	antimellin
Oleaceae	*Olea europaea*	4	lf	po	N	scopoletin
Poaceae	*Zea mays*	3	sy	po	N	coumarin
Polygonaceae	*Polygonum aviculare*	3	rt	–	N	–
Rosaceae	*Poterium ancistroides*	4	ap	po	?	tormentic acid
Scrophulariaceae	*Capraria biflora*	3	lf	po,ip	T	–
Scrophulariaceae	*Rehmannia glutinosa*	3	rt	po	N	rehmannioside D, rehmanin
Scrophulariaceae	*Scoparia dulcis*	3	wp	po	?	–
Urticaceae	*Urtica dioica*	5	wp	po	N	–

The information is drawn mostly from NAPRALLERT database, College of Pharmacy, University of Illinois at Chicago, USA. *ETH* number refers the number of countries where the plant is used as traditional medicine to treat diabetes. *Part tested*: ap: areal part, bl: bulb, fl: flower, fr: fruit, gm: gum, lf: leaf, rb: root bark, rt: root, rz: rhizome, sb:stem bark, sd: seed, st: stem, sy: style, wp: whole plant; *Toxicity*: T: toxic, N: nontoxic (Marles and Fransworth, 1995).

DISCUSSION

In the present review, an attempt was made to list up the plants which are used by the people as an ethnomedicine in three or more countries. Fourty seven medicinal plants are found as the antidiabetic drugs used in three or more countries (Table 1). A very few plants (13 plants) were studied in the clinical trail (Table 2). Many of the plants are used widely as the traditional medicine but no clinical trial record were found. It is interesting to know that Momordica charantia fruit is used in more than 12 countries but so far only two clinical trails are reported. Other widely used plants are Catharanthus roseus and Anacardium occidentale which are used in 10 and 9 countries, respectively and interestingly, no clinical trail report was found. Other widely used traditional antidiabetic drugs were Lupinus albus, Allium cepa, Allium sativum, Aloe vera, Eucalyptus globulus, Syzygium cumini. The Frati et al. performed clinical trial on Opunita streptacantha, and found acute hypoglycemic effect on NIDDM but without blinding or randomization effect (Ernst, 1997). There are several constituents for their alleged hypoglycemic effect reported from the antidiabetic plants (Table 1). The detail study on them would also be an important line of research.

Table 2: Antidiabetic Plants Tested Clinically

Family	Scientific name	Sample	Dose	Reference
Asclepiadaceae	*Gymnema sylvestre*	22 NIDDM	400 mg plant ext/d for 18-20 M	Baskaran et al. (1990)
Cactaceae	*Opunita streptacantha*	14 NIDDM 14 HV	500 g	Frati et al. (1990)
Cactaceae	*Opunita streptacantha*	8 NIDDM 6 HV	500 g broiled stem 2x500 g hourly	Frati et al. (1991)
Cactaceae	*Opunita streptacantha*	26 NIDDM	500 g broiled stem	Frati-Munari et al. (1988)
Cactaceae	*Opunita streptacantha*	8 NIDDM	100, 300 & 500 g broiled stem	Frati-Munari et al. (1988a)
Cactaceae	*Opunita streptacantha*	8 NIDDM	500 g broiled stem	Frati-Munari et al. (1988b)
Cactaceae	*Opunita streptacantha*	24 NIDDM	30 cap/d	Frati-Munari et al. (1992)
Cucurbitaceae	*Momordica charantia*	9 NIDDM	a) 50 ml fruit juice b) 230 g fried fruit	Leatherdale et al. (1981)
Cucurbitaceae	*Momordica charantia*	NIDDM	?	Welihanda et al. (1986)
Fabaceae	*Acacia coriacea*	6 HV	18 g flour	Thorburn et al. (1987)
Fabaceae	*Bauhinia forficate*	6 NIDDM	3 g leaf/d, for 56d	
Fabaceae	*Trigonella foenum-graecum*	21 NIDDM	15 g ground seed in meal	Madar et al. (1988)
Liliaceae	*Aloe barbadensis*	5 NIDDM	½ tea spoon/d for 4-14 weeks	Ghannam (1986)

Family	Scientific name	Sample	Dose	Reference
Liliaceae	*Allium cepa*	6 HV	125 mg essential oil/kg bw	Augusti et al. (1975)
Liliaceae	*Allium sativum*	30 HV	800 mg dried powder for 35 d	Kiesewetter (1991)
Moraceae	*Artocarpus heterophyllus*	?	20 g/kg bw	Fernando et al. (1991)
Acanthaceae	*Asteracanthus longifolia*	?	20 g/kg bw	Fernando et al. (1991)
?	*Cynara scolymus*	3 NIDDM	150 g mashed plant/d	Mescherikova et al. (1995)
Myricaceae	*Myrica uniflora*	18 NIDDM	3 g leaf/d for 56 d	Russo et al.(1990)

A Medline search was conducted (mesh headings, diabetes, hypoglycemic, plants, herbs, phytomedicine). All abstracts thus found were uncanned for clinical trails. Publication related to case reports or historical uses were discarded. Papers in any languages other than English, French or German were excluded. HV: healthy volunteer; NIDDM: Noninsulin Dependent Diabetes Mellitus (Ernst, 1997).

COMMENT

Phytomedicines are frequently used as treatment for diabetes in many cultures (Eisenberg et al., 1993; Bailey et al., 1989; Rahman et al., 1989; Bever et al., 1979; Jahodar, 1993; Lin, 1992; Yaniv et al., 1987). More than 1200 species of plants have been used traditionally or studied for their alleged hypoglycemic effects (Marles and Fransworth, 1995). There are more than 1500 prescription suggested for the clinical use in traditional Chinese medicine. It is interesting to note that with only a few exceptions, there are no attempts of replicating the results. Similarly, results from previous studies (Bever et al., 1979) have not been followed up. There are so many researches to find antidiabetic drugs but not a single herbal medicine is accepted clinically in general. The question is why? It is not that people are not using. It is not that doctors are not suggesting. It is not that patients are not benefiting from the herbal treatment. The main problem is that there is no any study in details on any particular herbal medicines in depth. Herbal medicines are not properly described for their doses, mode of administration, action mechanism, risk and benefit, bioavalbility, which are very important to be used for the clinical trial.

Some of the remedies are known to be associated with potential risk. Momordica charantia, for instance, has recently been shown to be hepatotoxic in rats (Tannekoon, 1994), however, it is widely used vegetable in the many of the Asian countries. Hypoglycemic coma has been reported after an overdose of Momordica charantia (Hulin et al., 1988). The risk-benefit, quality, doses, use for typical diabetic condition have not been reported any where. Such trend of research defame the herbal treatment. In addition to this, the safety issue is further complicated by the fact that non-medically trained herbalists may give incomplete advice to diabetic patients seriously endangering their health (Gills et al., 1994; Zimmer et al., 1994).

There are already several scientific evidences for the cause of diabetes mellitus and one major cause is the gradual destruction of insulin-producing β-cells in the pancreas. On this regard, the role of glutamic acid decarboxylase(GAD)-65, Insulin receptor substrate (IRS), Th1 and Th2 cells activities, and reactive oxygen spices (ROS) including SOD-activity, on diabetes mellitus have been studied. Vitamin C, vitamin E, nicotinamide, lipoic acid, N-acetyl-L-cysteine are some of the substances showing the preventive action on diabetes. However, there is no systematic study on the role of natural medicines and their actions in preventing diabetes. Therefore, besides hypoglycemic activity, protection to β-cells in the pancreas, regeneration of β-cells, are also important line of researches of antidiabetic plants.

At present, no antidiabetic phytomedicine can be recommended for clinical use. Rigorous investigation, preferably through randomized controlled trails could however prove to be fruitful. Twenty first century demands a systematic research on natural medicine to provide potential evidence based antidiabetic drugs.

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