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Review

Traditional medicinal plants of Manipur as anti-diabetics

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Manipur, which lies in the North-eastern part of India, is rich in its flora and fauna; and is one of the hotspots of biodiversity. The flora of this region includes aromatic and medicinal plants with a number of bioactive compounds. Before the coming of the modern pharmacological medicines, the people of Manipur use medicinal plants for the treatment of diabetes mellitus. Even today, people not only in the rural areas but those living in the urban areas are also using these traditional medicines, and give first preference to herbal treatments by consulting the medicine men. An outline of the medicinal plants of Manipur which are used for curing diabetes is reported.

Key words: Traditional, plants, Manipur, anti-diabetics.

INTRODUCTION

Since ancient times, plants have been used as herbal medicines. Ayurveda has a 5000 years old rich heritage of role of the use of plants in the treatment of various human ailments as alternative medicines. The ethno-botanical information reports about 800 plants that may possess anti-diabetic potential. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of diabetes mellitus (DM). DM can be defined as a group of syndromes characterized by hyperglycemia altered metabolism of lipids, carbohydrates and proteins along with an increased risk of complications from vascular disease. In simple terms, diabetes can be defined as a chronic disorder of metabolism caused by a relative or absolute lack of insulin in the body. Its primary characteristic is a high level of sugar in the body, in the fasting and/or post meal stages. During the normal digestion process, the body turns the food consumed into glucose and the insulin hormone helps the glucose so generated to reach the body cells. However, in diabetics, due to inadequate insulin - and its inadequate action, as a result - the glucose stays in the blood. Though several hormones are involved in the maintenance of diabetes, the most important ones are insulin and glucagon.

Diabetes is caused as a result of the loss of the balanced effect of these hormones, usually due to less insulin production, sugar starts accumulating in the blood and blood-sugar level increases and sugar passes in urine along with other minerals. High blood-sugar level is known as “hyperglycemia” and the presence of sugar in the urine is known as “glycosuria”. Insulin is secreted by β-cells of islets of Langerhans of pancreas and is necessary for the burning of sugar in the tissues with the help of oxygen. Thus, DM is a group of syndromes characterized polydipsia (drinking large amount of water), polyuria (excretion of large amount of dilute urine) and glycosuria (excretion of glucose in urine).

INTERNATIONAL STATUS OF DM

Knowledge about DM existed in ancient Egypt and Greece. The word ‘diabetes’ is derived from the Greek word “Diab” (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); ‘mellitus’ is the Latin word for “sweetened with honey” (refers to the presence of sugar in the urine). Earliest reference about a disease with ‘polyurea’ was made in “Ebers Papyrus” (Egypt), a document outlining clinical symptoms of the disease (1550 BC). Greeks had a knowledge of a disease (Celsus, 30-38 AD) accompanied by polyurea and wasting of body, whereas Aretaeus of Cappadocia (150 AD) mentioned a disease characterized by thirst and

polyurea which was christened as Diabetes. Subsequently, the knowledge permeated to Chinese (Tehang Tehong King, 200 AD), Iranians (Rhazes (860-932 AD) and Arabians (Avicena, 980-1037 AD).

From the Middle East, the knowledge of DM had spread into Spain (Mermonides, 1135-1204 AD) as a disease characterized by polyurea, polydipsia with sugary flavoured urine. With discovery of sugar in urine (Thomas Wills, 1664 AD) and its detection by laboratory test (Mathew Dobson, 1776 AD), the knowledge permeated into 18th century. Today, around 30 million people throughout the world suffer from DM. It is the most common metabolic abnormality in the world. Non-insulin dependent diabetes mellitus (NIDDM) is the most common form of diabetes constituting nearly 90% of the diabetic population in any country. Its prevalence varies in different geographic regions and also in different ethnic groups.

NATIONAL STATUS OF DM

The term Diabetes mellitus was recognized as 'Madhumeha', a type of 'Prameha', in primeval times. The knowledge of the system of DM existed with the Indians since prehistoric age. Its earliest reference (1000 BC in the Ayurbedic literature) was found in mythological form where it is said to have originated by eating Havisha, a special food which used to be offered at the times of Yagna organized by Daksha Prajapati. The disease was known as 'Asrava' during vedic era (600 BC) and a detailed description of it is available in Brahatta, viz. Charak Samhita, Sushruta Samhita and Vagbhatta. Asthanga Haridaya (600 AD) is the first medical treatise in which one gets clear definition of 'Madhumeha' by mentioning glycosuria (madhviv mehati - honey like urine). The word, 'Prameha' is derived from the root 'miha sechane' meaning watering. In reference to disease of human beings, it may have a meaning of passing urine, qualified by prefix 'pra' meaning excess in both frequency and quantity. Thus, 'Prameha' means 'Pra' (excessive)-'Meha' (urination).

According to ancient Hindu physicians, 'Madhumeha' is a disease in which a patient passes sweet urine and exhibits sweetness all over the body, that is, in sweat, mucus, breath, blood, etc. They knew of the fact that the urine of a Madhumeha patient tastes sweet. They had recorded in their observations that - 'if too many ants swarm around a spot of urine, one can state that Prameha of any variety, if neglected, will finally lead to Madhumeha and in due course become incurable'. It is interesting to note that although symptoms of the disease were known to ancient Hindu physicians, clear cut knowledge about the treatment of the disease was not handy although suitable dietary therapy, that is, use of oils (unsaturated fat) instead of animal fat (saturated fat), was recommended. It is evidenced by the fact that as early as Charak-Susruta era (600 BC), it was recommended that addition and restriction of certain foods were an adjunct to treatment of Madhumeha (Grover and Vats, 2001). It was recommended that the low carbohydrate diet (low sugar - low starch) and almost total withdrawal of animal fats should be taken recourse to by patients suffering from Madhumeha. However, it was also felt that lean and young patients should be prescribed nourishing diet, whereas obese adults should live on low calorie diet. Use of vegetable oil was generally recommended. The severity was high in urban areas and many cases go unreported due to lack of education on the disease as it is not contagious like malaria or tuberculosis. According to the India Council of Medical Research (ICMR), it had reported a prevalence of 2.3% in the urban and 1.5% in the rural areas. According to a report came from the multicentre study conducted by the ICMR, the estimated burden of Diabetes in India was 22 millions in 1990, 28 million in 1995 and 33 millions in 2000. It is a very large and continuously growing health problem and adequate treatment is often not available.

TYPES OF DIABETES MELLITUS (DM)

There are two types of Diabetes mellitus – Type 1, "Juvenile Diabetes mellitus" (Insulin Dependent Diabetes Mellitus, IDDM), which is hereditary and is treated by giving insulin; and Type 2, "Adult type" (Non-Insulin Dependent Diabetes Mellitus, NIDDM), which occurs in elderly people and is treated by controlling the diet and oral anti-diabetic drugs should be given. The main symptoms of these types of diabetes are, increased thirst, increased urinary output and ketonaemia and ketouria, that is, presence of ketone bodies in the blood and urine. Diabetes should be suspected when any of the symptoms are present. If there is any history of diabetes in one's family, then an individual should check for diabetes.

In the insulin dependent diabetes mellitus (IDDM), people do not produce insulin and have to take it every day to filter out the glucose from their blood and into their cells as fuel. Here, sometimes there is damage to the pancreas, the organ that produces insulin. IDDM is not associated with obesity and is complicated by ketosis (that is, piling of ketone bodies in the blood stream) and acidosis. In type II diabetes (NIDDM), the amount of insulin that is produced is not enough or the cells of the body do not respond to its presence. NIDDM is usually associated with normal β-cell morphology and insulin content, if the β-cells have not become exhausted. Obviously, the former kind is more severe and the later is more common especially in developing countries such as India.

Thus, in IDDM, a high blood sugar level due to failure of the β-cells in the pancreas is found whereas in NIDDM, a high blood sugar level due to failure of cells to take up

glucose is found. The exact causes of pancreatic failure and loss of cellular acceptance of insulin are unknown, but are associated with disease, environmental, and/or dietary conditions.

Human insulin

Human insulin, which is secreted by beta cells of the islets of langerhans of pancreas, is a polypeptide, having a molecular weight of about 6,000. It consists of two amino acid chains A and B, which are linked by two disulphide (–S–S–) linkages between cys (cystidine) 7 of A with cys 7 of B, cys 20 of A and cys 19 of B, and an intra -S-S- linkage between cys 6 and cys 11. The chain A contains 21 amino acids and chain B contains 30 amino acids, all in a known sequence; hence it is a polypeptide chain having 51 amino acids. The disulphide bridges are essential for its biological activity. Normal human pancreas contains about 8-10 mg of insulin. Insulin is an amphoteric protein and forms salts with weak acids and alkalis. It is soluble in water. It can combine with proteins such as protamine and with zinc without any change in its biological activity.

It is inactivated by digestive enzymes; hence it is not suitable for oral administration. The free amino and aliphatic hydroxyl groups of insulin are not required for biological potency. The solubility of insulin depends on its physical state (that is, amorphous or crystalline), on the concentration of zinc and on the nature of buffer in which it is being suspended. All tissues have the ability to metabolize insulin, but 80% of exerted insulin is normally degraded in the liver and kidneys. The amount of insulin secreted per day in a normal human is about 40 units (286 mmol). In normal individuals, insulin secretion is low between meals and increase with each meal. Duplication of pattern of secretion can be achieved in diabetes with portable electronic insulin pumps programmed to inject. Following intravenous insulin administration, the decline is maximal in about 30 min; following the subcutaneous administration, it is maximal in 2-3 h. The dose of insulin required to control the diabetes varies from patient to patient and from time to time in the same patient.

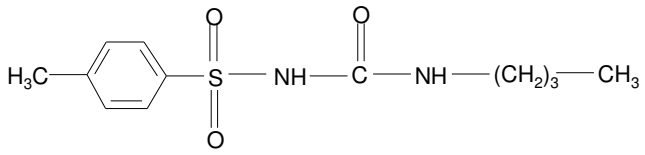
Diagnostic tests for Diabetes in urine and blood

Diabetes can be detected by the glucose tolerance test (GTT), which divides diabetes according to the sugar level of the patient as normal, mild, moderately severe, or severe diabetes. Diagnostic tests for diabetes in urine and blood are discussed here. There are two tests which are commonly used to show the presence of sugar in urine - (a) Benedict's test, and (b) Fehling's test. Among these two tests, Benedict's test is more satisfactory and is used more frequently. For Benedict's test: take 5 mL of Benedict's reagent in a test tube and add 5 mL of urine and mix. Heat the test tube for 5 min. in water bath and cool spontaneously. A greenish to yellowish brown to reddish brown precipitate is formed which shows the presence of sugar. A white precipitate may be produced due to the presence of phosphate, but this is not recorded. If the solution appears green due to the suspension of a yellow precipitate, then the presence of reducing substance or sugar is indicated as "trace". If the solution shows a yellow tinge, result is reported as '+', an orange precipitate as '++' and a brick red precipitate as '+++'.

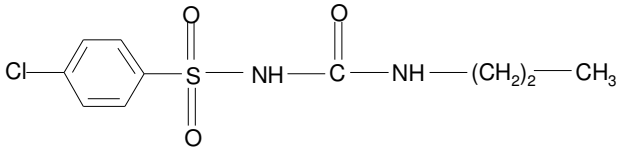
Blood glucose analysis is of great value in detection of diabetes. Due to hormonal control, blood sugar level is maintained constant at a value of 70-120 mg of glucose per 100 mL. Though several hormones are involved in this, the most important ones being insulin and glucagon. By diet control, the presence of sugar in the urine may come down to normal range. But this may not be so in the blood where the sugar level may be beyond the normal range. Thus, the severity of the diabetic condition, that is, when the blood sugar level is 160-180 mg/dL, can be known only by blood-sugar tests. One of the important blood sugar tests for detecting the diabetic condition is the sugar tolerance test or glucose tolerance test (GTT). This test is usually carried out in the morning after a night's fast but, if necessary, it may be done some four or five hours after the last food was taken. Blood samples are taken for the determination of fasting blood sugar. After withdrawing the blood sample, the patient is orally given 1.75 g of glucose/kg body weight and blood samples are taken subsequently at half, one and two hours intervals and the blood sugar level is determined. In the normal case, the blood sugar level rises to about 150 after an hour, then starts falling and at the end of two hours, the normal level is restored. In diabetic condition, the sugar level rises higher at 200-300 mg and stays high for a longer time, i.e., 3-6 h. Further, the peak value is reached in longer time (2 h). In non-diabetics, the peak of the curve is usually between half and one hour. For estimation of sugar, sodium fluoride (100 mg/mL) has to be added to the blood immediately after collection. This is done to inhibit blood enzymes which alter the amount of glucose in blood during storage. Within limits, however, the glucose concentration of blood in the body responds to a variety of biochemical and physiological events. Such factors as stress, size and sugar content of meals, rate of digestion, and agents that alter glucose absorption and metabolism allow sugar levels to be modified at several points throughout the glucose cycle in the body.

Hypoglycemic drugs

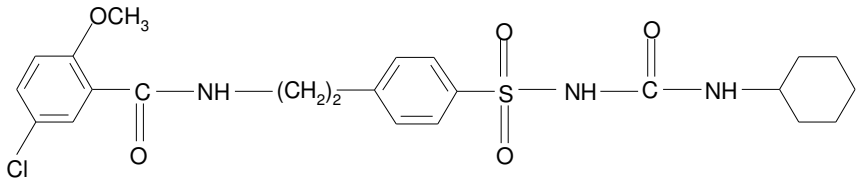
If diabetes is properly controlled, a diabetic patient can live a normal long life. Diabetes can be controlled by stabilizing the body metabolism. Control of diabetes should be continued for years. The diet control is of



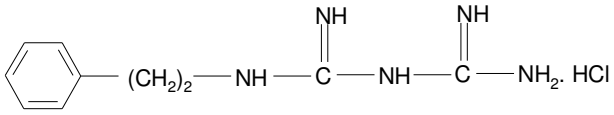
Tolbutamide, 1-butyl-3-tosyl urea



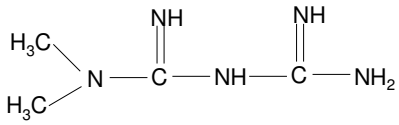
Chlorpropamide, 1-(4-chlorobenzenesulphonyl)-3-propyl urea



Glybenclamide, 4-(2/-[5/-chloro-2-methoxybenzamido]ethyl)benzene-sulphonyl-3-cyclohexyl urea



Phenformin hydrochloride, 1-phenethyl biguanide



Metformin, N,N - dimethyl biguanide

Figure 1. sulphonylureas and biguanides

immense importance in controlling diabetes and should be maintained life long. If the diet of the diabetes is not properly controlled, insulin or oral hypoglycemic drugs will not control the disease properly. A diabetic person should control his or her body weight and should avoid overeating. Regular exercise should be included in daily routine as the muscles live on glucose and exercise helps them to utilize it. Diabetic patients are more vulnerable to infectious skin diseases like boil, carbuncles, etc. These infections must be attended immediately and proper care should be taken.

The drugs which lower the blood sugar and can treat the symptoms of DM are known as hypoglycemic drugs. These drugs could be categorized as (i) insulin and insulin preparation, which are employed only parenterally, and (ii) oral hypoglycemic drug which can be administered orally. As insulin are ineffective through oral administration, oral hypoglycemic drugs are introduced which could control diabetes when administered orally. Although the drugs available now do not meet all the requirements, but the most important drugs belong to two groups, namely, sulphonylureas and biguanides (Figure 1).

Sulphonylureas are useful in treating diabetes which can not be controlled by diet alone. These drugs can be used to treat mild diabetics during pregnancy. Sulphonylureas are quickly absorbed from the intestinal track. These drugs are ineffective in Juvenline diabetes, and in presence of ketosis and during severe stress. Some important drugs of this group are tolbutamide, chlorpropamide, glybenclamide, tolazamide, etc.

Biguanides control all types of DM. These drugs reduce glucose absorption from the intestine. These drugs can be used to treat mild diabetes during pregnancy. Though these drugs are not used in treating Type I, but it is used along with insulin to control Type I. These drugs which have been used as oral hypoglycemic agents do not affect insulin secretion but lowers the blood sugar in diabetics by directly increased the uptake of glucose by cells and by actively promoting its glycolysis via the Embden Mayerhof (pathway to pyruvate and lactate). Some important drugs of this group are phenformin and metformin, which can be obtained from *Zingiber officinale*.

PLANTS THAT SHOW HYPOGLYCEMIC ACTIVITY (HERBAL ANTI-DIABETICS)

Since ancient times, traditional medicines all over the world have advocated the use of plants to treat diabetes. The ethno-botanical information reports about 800 plants that may possess anti-diabetic potential (Alarcon et al., 1998). Main symptoms targeted were thrist, polyuria and glycosuria. Most of the drugs from plant sources are secondary metabolites which have no role in plant metabolisms but are postulated to play a significant role in the plant defense mechanism. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of NIDDM (Bailey and Day, 1989; Marles and Farnsworth, 1995). There are about 200 pure compounds from plant sources reported to show blood glucose lowering effect. The compounds may be alkaloids, carbohydrates, glycosides, flavonoids, steroids, terpenoids, peptides and amino acids, lipids, phenolics, glycopeptides and iridoids.

Many anti-diabetic products of herbal origin are now available in the market. Inolter is one of them; each capsule of Inolter contains Momordica charantia (fruits, seeds and leaves, 100 mg), Trigonella foenum graeceum (seeds, pods and leaves, 100 mg), Asphalt (100 mg), Gymnema sylvestre (Root and leaves, 100 mg) and Eugenia jambolena (seeds, fruits and bark). Inoltar is claimed to have properties of releasing of insulin from islet of langerhans and as an insulin sensitizer (Shanmugasunderam et al., 1990). A scientific clinical trial has been conducted to study the role of Inoltar (herbal product) in the management of type 2 diabetes (Kothari et al., 2002). Several herbs have shown anti-diabetic activity when assessed using presently available experimental techniques (Saifi et al., 1999). Although, oral hypoglycemic agents/insulin are the mainstay of treatment of diabetes and are effective in controlling hyperglycemia, they have prominent side effects and fail to significantly alter the course of diabetic complications (Rang and Dale, 1991).

More than 1200 species of plants have been screened for activity on the basis of ethnopharmacology or on random basis. The products obtained range from marine algae and fungi to phytogenetically advanced classes of compounds. Plants that demonstrate hypoglycemic activities within the body play a major role in folk medicine, and various studies on folklore have identified approximately 50 plants that affect the sugar level in blood.

Manipur, which lies in the North-eastern part of India, is rich of its flora and fauna; and is one of the hotspots of biodiversity. The flora of this region includes aromatic and medicinal plants with a number of bioactive compounds. Most of these medicinal plants are required to identify the active principles present in these plants. Before the coming of the modern pharmacological medicines, the people of Manipur is using medicinal plants for the treatment of DM. Even today, people not only in the rural areas but those living in the urban areas are also using these medicines, and give first preference to herbal treatments by consulting the medicine men. A report of some commonly used anti-diabetic plants which are found in Manipur, North-East India in the indigenous system of health care is given below.

Acacia arabica or nilotica

Feeding of 94% seed diet to normal rats showed significant hypoglycemic effect versus controls. However, the same diet failed to show any hypoglycemic effect in alloxanized rats (175 mg/kg SC) indicating that plant acts through release of insulin (Singh et al., 1975). Powdered seeds of *A. arabica* administered in doses of 2, 3 and 4 gm/kg body weight exerted a significant hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells. No acute toxicity and behavioral changes were observed at these doses (Wadood et al., 1989).

Aegle marmelos

Oral administration of aqueous decoction of Aegle marmelos root bark (1 ml/100 gm) showed hypoglycemic effect which was maximum (44%) at 3 h in normal fasted rats. In addition, the same extract completely prevented peak rise of blood sugar at 1 h in OGTT. The hypoglycemic activity was reduced upon storage of extract (Karunanayake et al., 1984). Aqueous extract of the leaves (1 gm/kg for 30 days) significantly controlled blood glucose, urea, body weight, liver glycogen and

serum cholesterol of alloxanized (60 mg/kg IV) rats as compared to controls and this effect was similar to insulin treatment (Ponnachan et al., 1993). When fed as aqueous leaf extract (1 gm/kg/day) to STZ (45 mg/kg IV) diabetic rats for 2 weeks, it decreased malate dehydrogenase levels (an enzyme known to increase in diabetes) in comparison to diabetic controls. The extract was equi-effective in comparison to insulin in restoring blood glucose and body weight to normal levels (Seema et al., 1996). Aqueous leaf extract administered orally for 28 days also normalized STZ (45 mg/kg body weight) induced histo-pathological alterations in the pancreatic and kidney tissues of rats (Das et al., 1996).

Allium cepa

Various ether soluble fractions of onion as a single oral dose (0.25 mg/kg) showed significant hypoglycemic effect in normal fasted rabbits. Ether extract showed most potent hypoglycemic action (Augusti, 1973). Petroleum ether insoluble fraction of the ether extract of dried onion powder (100 mg/kg) given orally for 7 days to alloxanized (180 mg/kg) diabetic rabbits caused a significant anti-hypoglycemic effect (Mathew and Augusti, 1975). In a preliminary study of seven different fractions obtained from onion bulb, only petroleum ether and chloroform extracts significantly lowered blood sugar in OGTT (2 mg/kg) in rabbits (Gupta, 1977).

Administration of a sulphur containing amino acid isolated from *A. cepa*, called S-methyl cysteine sulphoxide (SMCS) to alloxanized rats significantly controlled blood glucose and lipids in serum and tissues, and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG CoA reductase. The effect was comparable to that of glibenclamide and insulin (Kumari et al., 1995).

Allium sativum

Oral administration of 0.25 mg/kg of ethanol, petroleum ether, ethyl ether extract of *Allium sativum* causes 18.9, 17.9, 26.2% reduction in blood sugar in alloxan- diabetic rabbits (150 g/kg IV) (Jain and Vyas, 1975). Oral administration of 0.25 gm/kg allicin (isolated from A. sativum) produced hypoglycemia comparable to tolbutamide in mildly diabetic animals (Mathew and Augusti, 1973). Pretreatment with aged garlic extract (AGE) in stress induced hypoglycemia model of mice significantly prevented adrenal hypertrophy, hyperglycemia and elevation of cortisone without altering serum insulin levels. The efficacy of AGE was the same as that of diazepam. Thus, AGE may prevent stress-induced risk of DM and its progression (Kasuga et al., 1999). Administration of S-allyl cysteine sulphoxide (SACS), a sulphur containing amino acid, significantly decreased the concentration of serum lipids, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver glucose 6-phosphatase. It also significantly increased liver and intestinal HMG CoA reductase activity and liver hexokinase activity (Sheela and Augusti, 1992). In another study, oral administration of SACS to alloxan-diabetic rats for one month ameliorated glucose intolerance, weight loss, depletion of liver glycogen in diabetic rats in comparison to glibenclamide and insulin (Sheela et al., 1995).

Aloe vera* or *Aloe barbadensis

It is used in Ayurveda for managing painful conditions and is also mentioned in folk medicine of Arabian Peninsula for management of diabetes. Extracts of aloe gum effectively increased glucose tolerance in both normal and diabetic rats (Al-Awadi and Gumma, 1987). Chronic but not single administration of the exudates of the leaves of *A. barbadensis* showed significant hypoglycemic effect in alloxan-diabetic mice. However, single as well as chronic administration of the bitter principle showed significant hypoglycemic effect in the same model. The hypoglycemic effect of single dose of the bitter principle was extended over a period of 24 h with maximum hypoglycemia observed at 8 h while chronic administration (exudates twice daily and the bitter principle once a day for 4 days) showed maximum reduction in plasma through glucose level at the 5th day. Hypoglycemic effect of *A. vera* and its bitter principle is mediated through stimulation of synthesis and/or release of insulin from the beta-cells of Langerhans (Aiabnoor, 1990).

Artemisia pallens

It is also used in folk medicine as a treatment for DM in parts of South India.26 Oral administration of methanol extract of aerial parts A. pallens showed a dose-dependent (100, 500 and 1000 mg/kg) anti-hyperglycemic effect in glucose fed hyperglycemic and all oxanized rats (60 mg/kg IV). The effect was moderate in fasted normal rats but more in diabetic rats (Subramonium et al., 1996).

Areca catechu

An epidemiological study has shown that nitrosamines released during betel chewing may contribute to the risk of developing NIDDM (Mannan et al., 2000). Subcutaneous administration of alkaloid fraction of A. catechu (0.05-0.5 mg/kg) in alloxanized rabbits (140 mg/kg of body weight) had shown significant hypoglycemic effect lasting for 4-6 h (Chempakam, 1993).

Azadirachta indica

Alcoholic extract of *Azadirachta indica* showed hypoglycemic and anti-hypoglycemic effect in normal, glucose fed and STZ diabetic rats (Chattopadhyay et al., 1987). The plant exerts its pharmacological activity independent of its time of administration, that is, either prior or after alloxan administration (Khosla et al., 2000). The plant blocks the action of epinephrine on glucose metabolism, thus increasing peripheral glucose utilization (Chattopadhyay, 1996). Bitter principles – nimbin, nimbinin and nimbidin – were isolated from this plant.

Beta vulgaris

Various glycosides isolated from the root extract of *B. vulgaris* have been shown to increase glucose tolerance in OGTT conducted in rats (Yoshikawa et al., 1996). In addition, the extract also inhibited non-enzymatic glycosylation of skin proteins in STZ diabetic rats (Tunali et al., 1998).

Biophytum sensitivum

The leaf extract of the plant has been shown to exert significant anti-hyperglycemic effect in alloxanized rabbits possibly by pancreatic cells stimulating action as the plant was effective in only mild to moderate and not in severe diabetes (Puri and Baral, 1998).

Bombax ceiba

A C-flavonol glucoside isolated from B. ceiba leaves called as Shamimin has been shown to exert significant hypoglycemic activity at the dose of 500 mg/kg in rats (Saleem et al., 1999). The extract was lethal in rats at 500 mg/kg but not in mice even up to 1 gm/km dose.

Brassica juncea

Oral feeding of *B. juncea* diet (10% w/w) for 60 days to normal rats led to significant hypoglycemic effect. This effect was attributed to stimulation of glycogen synthetase (leading to increase in hepatic glycogen content) and suppression of glycogen phosphorylase and other gluconeogenic enzymes (Khan et al., 1995).

Caesalpinia bonducella

The aqueous and alcoholic extract of *C. bonducella* seeds exhibited significant hypoglycemic and antihyperglycemic activities in normal and STZ hyperglycemic rats. However, aqueous extract was associated with prolonged hypoglycemia as compared to ethanolic extract. Hypolipidemic activity has also been described (Sharma et al., 1997).

Cajanus cajan

It is also used in Panamanian folk medicine for the treatment of diabetes. A single dose of un-roasted seeds of *C. cajan* administration as a 60 and 80% diet to normal and alloxanized mice caused a significant reduction in the serum glucose levels after 1-2 h and a significant rise at 3 h. On the other hand, roasted seeds administration caused a significant increase in the serum glucose levels during a 3 h experimental period. Roasting of seeds at high temperature for 30 min resulted in the total loss of hypoglycemic principle but not the hyperglycemic principle present in the seeds (Amalraj and Ignachimuthu, 1998). Cooked diet of *C. cajan* has also shown significant hypoglycemic effect in healthy human volunteers (Panlasigui et al., 1995).

Capparis decidua

Oral feeding of diet containing (30%) *C. decidua* fruit powder for 3 weeks to alloxanized (80 mg/kg IP) diabetic rats (blood glucose, 450 mg %) showed significant hypoglycemia (blood glucose, 120-130 mg %) (Yadav et al., 1997).

Citrullus colocynthis

The fruit of this plant is traditionally used as anti-diabetic in Mediterranean part of the World. Aqueous extract of its fruit showed dose-dependent increase in insulin release from isolated islets (Abdel-Hassan et al., 2000). Oral administration of aqueous extract (300 mg/kg) in normal rabbits significantly reduced plasma glucose after 1 h and highly significant reduction after 2, 3, and 6 h. Glycosidic extract (50 mg/kg) was more effective in lowering fasting glucose as compared to alkaloid extract. Graded doses (10, 15 and 20 mg/kg) of saponin also reduced plasma glucose concentration in alloxanized rabbits. Thus, saponins and glycosidic components of *C. colocynthis* are responsible for its hypoglycemic effect (Abdel-Hassan et al., 2000).

Coccinia indica

It is used in Ayurveda and Unani system of medicine for treatment of diabetes, skin eruptions, tongues sore, earache, etc (Chopra et al., 1956). Feeding of water soluble alkaloid extract of *C. indica* leaves to normal

fasting guinea pigs showed hypoglycemic activity of short duration and the effect was attributed to the presence of β-sitosterol (Mukherjee et al., 1972). Oral administration of pectin isolated from *C. indica* fruit showed a significant hypoglycemic action in normal rats due to stimulation of glycogen synthetase activity and reduction of phosphorylase activity (Kumar et al., 1993).

Oral administration of 500 mg/kg of *C. indica* leaves showed significant hypoglycemia in alloxan-diabetic dogs (45 mg/kg IV) and increased glucose tolerance in normal and diabetic dogs (Singh et al., 1985). Oral administration of ethanolic extract of *C. indica* to normal rats significantly lowered blood sugar in fasted model and depressed the peak value in glucose loaded model (Chandrasekar et al., 1989). Oral feeding of ethanol extract of the leaves (200 mg/kg) to 18 h fasted rats and STZ diabetic rats led to lowering of blood sugar by 23 and 27%, hepatic glucose-6-phosphatase by 19 and 32% hepatic fructose-1,6-bisphosphatase by 20 and 30%, respectively, as compared to controls (Shibib et al., 1993). Oral administration of water soluble alkaloid fraction, chloroform extract and alcoholic fraction (100 mg/kg) reduced fasting blood glucose of guinea pig by 29.3, 34.5 and 36.3%, respectively. Blood glucose was reduced by 25 and 21% by chloroform extract and alkaloid fraction, respectively, in OGTT (1 gm/kg) conducted on rats (Mukherjee et al., 1972).

Beneficial effects of leaves of *C. indica* have also been shown in a double-blind control trial controlling 16 patients with uncontrolled maturity onset diabetes and 16 controls. Treatment was given for 6 weeks and 10 patients showed marked improvement in their glucose tolerance (Azad et al., 1979). In a clinical study (n=30), oral administration of dried extract of *C. indica* (500 mg/kg for 6 weeks) significantly restored the raised activity of lipoprotein lipase and the levels of G-6 phosphotase and LDH, which are otherwise increased in the severe diabetics. This action of the plant extract was akin to that of insulin (Kamble et al., 1998). As a single oral dose, the plant extract has been shown to exert beneficial hypoglycemic effect in experimental animals and human diabetic subject possibly through an insulin screening effect or through influence of enzymes involved in glucose metabolism. It was suggested that the hypoglycemic effect of *C. indica* are partly mediated through suppression enzyme glucose-6-phosphotase (Hossain et al., 1992).

Curcuma caesia

The rhizome of *C. caesia* is used traditionally by the people of Manipur (Warjeet et al., 2006).

Euccalyptus globulus

It is a lofty tree of about 90 cm in height and is grown in various parts of India. Aqueous extract of (0.5 gm/L of solution) of euccalyptus increased peripheral glucose utilization in the mouse abdominal muscle and stepwise enhancement of insulin secretion from the clonal pancreatic beta cell line by 70-160% (Gray and Flatt, 1998). Administration of *E. globulus* leaves diet (6.25% w/w) for 12 days to normal rats did not result in hypoglycemia. In addition, STZ administration to these pre-treated rats did not produce hyperglycemia as severely as it was seen in controls. In addition, pre-treated rats also showed less polydypsia and body weight loss.

Eugenia jambolana

It belongs to the family Myrtaceae. The fruits, that is, the seeds and the pulp are used as antidiabetics in Indian medicine since ages. The aqueous and alcoholic extract of seeds exhibited significant decrease in plasma glucose levels, upon chronic administration in diabetic rats (Grover et al., 200; Grover et al., 2001).

The possible mechanism suggested is the extract-induced enhancement of serum insulin levels by the pulp extract. The active principles isolated were a peptidoglycan, composed of 7-amino acids; and an oligosaccharide. It is found that the peptideglycan, due to its nature is not easily degraded. Also, modification of insulin by sugars might confer resistance to enzymatic degradation, while retaining the hypoglycemic activity of insulin. However, the structures of the two compounds obtained from the extract still remain to be elucidated (Kelkar, 1996).

Eupatorium birmanicum

The decoction of the leaves of the plant is used traditionally by the people of Manipur (Warjeet and Reena, 2007).

Eugenia uniflora

It is a large bushy shrub cultivated in garden. It is also distributed in Southern Asia, Africa, and in South America. Oral feeding of ethanol extract of the leaves of *E. uniflora* to mice has been shown to contain plasma glucose levels during OGTT and plasma triglyceride level in oral corn oil tolerance test (Arai et al., 1999). Few fractions isolated on the basis of polarity and molecular size from the ethanolic extract of the leaves of *E. uniflora* have shown positive effects in OGTT conducted in mice.

In addition, all fractions except one showed dose-dependent inhibitory effect on the lipase activity and these effects were apparently due to the inhibition of the decomposition of carbohydrates and fats in the intestine (Arai et al., 1999).

Ficus bengalenesis

A very large tree distributed throughout India from sea level to 1,200 m. A glucoside isolated from the bark of F. bengalenesis showed more potent hypoglycemic action as compared to crude ethanolic extract and the activity was half of tolbutamide (Augusti, 1975). Oral administration of bark extract showed significant anti-hyperglycemic effect in STZ diabetic rats by raising serum insulin levels or inhibiting insulinase activity in liver and kidney (Avhrekar et al., 1991). Oral administration of leucopelargonidin derivative isolated from bark of *F. bengalenesis* exerts significant hypoglycemic activity in normal and moderately alloxanized diabetic dogs (Augusti et al., 1994). A leucocyanidin derivative isolated from the bark of *F. bengalenesis* was hypoglycemic in normal rats.

Combination of single dose of this chemical and low dose insulin controlled diabetes in alloxanized rats as effectively as high dose of insulin. In addition, long term treatment with this combination showed equal response to double dose of insulin in respect to body weight, urine and blood sugar along with amelioration of serum cholesterol and triglyceride (Kumar et al., 1994). The other glycoside (pelargonidin derivative) isolated from bark decreased fasting blood glucose by 19% and improved glucose tolerance by 29% in moderately diabetic rats at the dose of 250 mg/kg. In comparison, glibenclamide (2 mg/kg) showed 25 and 66% reduction, respectively, versus controls (Cherian et al., 1992). Treatment with the same glycoside (100 mg/kg/day) for one month reduced the fasting blood glucose levels to almost half of the pretreatment levels. Glucose tolerance improved by 15% in glycoside treated group versus 41% in glibenclamide treated group (0.5 mg/kg/day).

In addition, pelargonidin was more potent than leucocyanidin in stimulating in vitro insulin secretion by beta cells (Cherian et al., 1992). Another glycoside, leucopelargonidin derivative possesses significant hypoglycemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats (Cherian et al., 1993). Upon single administration of 0.2-1.8 gm/kg and 100, 250, 500 mg/kg/day of the extract for one month in experimental animals, no lethality and toxic effects were observed.60 Leucodelphinidin (250 mg/kg) also showed hypoglycemic action equal to that of glibenclamide (2 mg/kg) in normal and alloxan-diabetic rats. However, in OGTT, it was less effective as compared to glibenclamide (2 mg/kg) Geetha et al., 1994).

Ficus hispida

The traditional use of F. hispida is the use of the bark in the treatment of DM. It is believed that the bark should be peeled out upward from the bottom of the plant and that peeling out of bark in downward manner is not effective in the treatment of the disease (Warjeet and Bimola, 2008). The important active components of F. hispida are β-sitosterol, β-sitosterol-α-D-(+)-glucoside, 10-ketotetracosylarachidate, 24-ketopentacosan-1-ol, 24-ketopentacosyl-γ-hydroxypentanoate, etc.

Gymnema sylvestre

The leaves of Gymnema sylvestre find use as antidiabetic remedy in ancient Indian medicine since 2000 years. The extract of leaf inhibited glucose absorption in small intestine of rats.

Kigelia pinnata DC

The decoction of the fruits of the plant is widely used for curing diabetes in Manipur (Bimola, 2006). The compounds isolated are found to be 7-hydroxyeuconomic acid, 7-hydroxyviteoid, 10-deoxyeucommidol, etc.

Melothria purpusila Cogn.

The decoction of the whole plant is used. Melothria purpusila is also used for curing jaundice (Warjeet et al., 2005).

Smilax lanceaefolia Roxb.

The rhizome of Smilax lanceaefolia is used, not only for diabetes but also for curing urinary calculi (Warjeet and Brajeshwari, 2010).

Mechanisms of action of herbal anti-diabetics

The breakdown of food into simple sugars that are absorbed into the blood stream begins in the mouth, where salivary amylases attack the long-chain, molecular carbohydrate components, releasing oligosugars. Further digestion of food particles occurs in the stomach and especially in the small intestine. When digestion is complete, the monosaccharides enter the blood vessels of the intestinal villi. Although, insulin release from the pancreas and sugar storage by the liver maintain sugar and salt balance in our body, any problem in the production or regulation of the hormones will manifest itself with problems with blood-sugar and fluid/salt imbalances. Herbal anti-diabetics are found to have properties of releasing of insulin from islet of langerhans and as an insulin sensitizer.

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