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Diabetes the Global Economic Burden of Adults and the Role of Herbalism as a safe & alternative cost-effective therapy: An updated overview

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Abstract

Diabetes is a major global health threat to the human health as the prevalence has rapidly increased over the past four decades. The costs of diabetes include both direct costs from medical care as well as indirect costs incurred through loss of productivity or earnings, both of which are important contributors to the global economic burden. Global trend with focus on green medicine serve as an important safe & alternative cost effective therapy as compared to allopathic medicine. Plants have their chemical compounds which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having antidiabetic effect. Herbalism is becoming focusing point due to research on herbs and their use in treatment of diabetes and its prevention The scientific study of traditional medicines, concerned medicinal plants are thus of great importance.

Keywords: Diabetes, Global economic burden, Cost-effective therapy, Herbalism

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Introduction

The term Diabetes was first coined by Apollonius of Memphis around 250 B.C, which literally meant "to go through" or siphon as the disease drained more fluid than a person could consume. Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar level, which causes congenital (type I insulin-dependent) or acquired (type II noninsulin-dependent) diabetes mellitus.[1] Diabetes contribute 1.3 million deaths globally, but it is a major risk factor for other causes of death also and is therefore high attributable economic burden of disability as the synthetic drugs used for the treatment cause serious side-effects. Herbal drugs introduced with modern technology can lower economic burden besides being having high therapeutic index value.

The global burden of Diabetes Mellitus

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. In 1994, the International Diabetes Federation (IDF) Directory included type I and type II diabetes estimates supplied by member nations. Using these data, IDF estimated that over 100 million people worldwide had diabetes.WHO also produced a report using epidemiological information and estimated the global burden at 135 million in 1995, with the number reaching 299 million by the year 2025.[2] In the 2006 3rd edition of the Diabetes Atlas the estimates were of 246 million people worldwide with diabetes for 2007, and an anticipated 380 million for 2025. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.[3]The National Urban Survey conducted across the metropolitan cities of India revealed percentage of population affected by diabetes:11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India)[4] 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India).

Classification

The etiologic classifications of diabetes mellitus are listed below. Adapted from WHO and ADA[5,6]

Table 1: Etiological Classification of Diabetes

I. Type 1 Diabetes mellitus A. Autoimmune B. Idiopathic **II. Type 2 Diabetes mellitus** Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance **III. Other specific types of diabetes mellitus** A. Genetic defects in β-cell function 1. Chromosome 12, HNF-1α (MODY 3) 2. Chromosome 7, glycosidase (MODY 2) 3. Chromosome 20, HNF-4α (MODY 1) 4. Mitochondrial DNA 5. Monogenic diabetes **B. Genetic defects in insulin action** 1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipotrophic diabetes **C. Disease of the exocrine pancreas** 1. Pancreatitis 2. Pancreatectomy/trauma 3. Neoplasia 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalcific pancreatopathy **D. Endocrinopathies** 1. Acromegaly 2. Cushing syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronoma **i.Pharmacologically or chemically induced** 1. Vacor 2. Pentamidine	3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormones 6. Diazoxide 7. β-adrenergic agonists 8. Tiazides 9. Dilantin 10. α interferon **ii. Infections** 1. Congenital rubeola 2. Cytomegalovirus **iii. Infrequent forms of autoimmune diabetes** 1. Stiff-man syndrome 2. Antibodies against insulin receptors **iv. Other syndromes occasionally associated with diabetes** 1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Friedreich ataxia 6. Huntington's chorea 7. Lawrence-Moon-Biedel syndrome 8. Myotonic dystrophy 9. Porphyria 10. Prader-Willi syndrome **IV. Gestational diabetes mellitus** Occurs in mostly in women during gestation.

➢ Type I diabetes mellitus

Type I diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency[7] Type I is usually characterized by the presence of anti–glutamic acid decarboxylase, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta cell destruction. Eventually, all type I diabetic patients will require insulin therapy to maintain normoglycemia.

➢ Type II diabetes mellitus

Type II diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. Most individuals with Type II diabetes exhibit intra-abdominal (visceral) obesity, which is closely related to the presence of insulin resistance[8]**.** In addition, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often are present in these individuals. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in Blacks, Hispanics and Native Americans.

Clinical features of Type I and type II diabetes

a) Clinical features of Type I Diabetes

Some of the symptoms include weight, polyurea, polydipsia, polyphagia, constipation fatigue, cramps, blurred vision, and candidiasis[9]**.** Long lasting type I DM patients may be susceptible to microvascular complications.[10]and macrovascular disease (coronary artery, heart, and peripheral vascular diseases)[11]

b) Clinical features of Type II diabetes

Most cases are diagnosed because of complications or incidentally. Carries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity. Most patients with type II diabetes die from cardiovascular complications and end stage renal disease. Geographical variation can contribute in the magnitude of the problems and to overall morbidity and mortality[12,13]

Other specific types of diabetes

- **Genetic defects of the β-cell.**

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are

frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. [14]

- **Diseases of the Exocrine Pancreas**

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma

- **Endocrinopathies**

Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

Drug- or Chemical-Induced Diabetes

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic -cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids.

- **Infections**

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type I diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.[15,16]

- **Uncommon Forms of Immune-Mediated Diabetes**
- **Other Genetic Syndromes**

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of -cells at autopsy.

Gestational Diabetes Mellitus (GDM)

Pathogenesis of Diabetes

a) Pathogenesis of Type I Diabetes

Type I DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the β-cells cells are destroyed, hyperglycemia develops and Diabetes may be diagnosed. Currently, autoimmunity is considered the major factor in the pathophysiology of type I DM.

b) Pathogenesis of Type II Diabetes

Type II Diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat. A role of excess glucagon cannot be overestimated; indeed, type II is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting α cell and the insulin-beta cells lost, leading to hyperglucagonemia and hence the consequent hyperglycemia.

Complications of Diabetes Mellitus

1- Acute complications

- Hypoglycemia
- Hyperglycemic crises
- Diabetes Ketoacidosis (DKA)
- Hyperglycemic hyperosmolar state (HHS)

2- Chronic Complications

a) ***Micro vascular complications***

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy

b) ***Macrovascular disease***

3. Other Complications and Associated Conditions

- Impaired growth and development
- Associated autoimmune conditions like Hypothyroidism, Hyperthyroidism, Celiac disease, Vitiligo, Primary adrenal insufficiency (Addison's disease)
- Lipodystrophy (lipoatrophy and lipohypertrophy)
- Necrobiosis lipoidica diabeticorum
- Non-alcoholic fatty liver disease
- Infections seen in patients with diabetes
- Limited joint mobility

Management of Diabetes

The goal of diabetes management is to keep blood glucose levels as close to normal as safely possible. Since diabetes may greatly increase risk for heart disease and peripheral artery disease, measures to control blood pressure and cholesterol levels are an essential part of diabetes treatment as well.

Management of Type II Diabetes

a) Non-pharmacological Therapy

Non-pharmacological measures including diet, exercise and stress alleviation are as important interventions for the management of diabetes.

- **Medical Nutrition Therapy (MNT)**

A proper diet is important component of therapy in all patients with diabetes. In patients with Type II DM recommendations for caloric distribution is as follows: 55-60% energy from carbohydrate, 10-15% from protein and 20-25% from fats. This dietary distribution is also indicated in patients with type I diabetes on intensive insulin regimens

in whom near-normoglycemic control is less achievable on diets higher in carbohydrate content.

- **Dietary Fiber**

Fibers such as cellulose or hemicelluloses, as found in bran, termed as insoluble fibers increases intestinal transit time and may have beneficial effects on colonic function. Soluble fibers such as gums and pectin's, as found in beans, oatmeal, or apple skin, tend to decrease gastric and intestinal transit slowing glucose absorption thus decreasing hyperglycemia.

- **Artificial Sweeteners**

The nonnutritive sweetener saccharin is widely used as a sugar substitute. Aspartame may prove to be the safest sweetener for use in diabetics which is180 times as sweet as sucrose. A major limitation is its heat labiality, which precludes its use in baking or cooking. These should be used in moderation.

- **Fruits**

Fruits (whole) should be taken in moderation. However, very sweet fruits and fruit juices can be avoided.

- **Alcohol**

Alcohol intake is best avoided and if used must be in moderation as it may worsen the dyslipidemia, neuropathy and glycemic control.

- **Common Salt**

Up to 6 gms /day of are permitted. Restrict pickles, papad, chatni and salty processed foods.

- **Physical Activity**

In Type II DM exercise programme to achieve weight reduction and calorie counting is central to the management. The best form of exercise is a stepwise increase in aerobic exercises. All diabetics need to be evaluated to rule out any contraindication like proliferative diabetic retinopathy, autonomic neuropathy etc. before any exercise programme. Brisk walking for 30-60 minutes or equivalent should be enforced regularly. Yoga, a traditional Indian system, has been demonstrated to have beneficial effect in diabetes. Some aspects of Yoga like, Asanas (involving postures), Pranayama (involving breath), Dhayana (meditation) and Bhavana (visualization) are beneficial but need to be learnt under expert guidance.[17]

b) Pharmacological Therapy

1. Drugs that primarily stimulate insulin secretion, known as *insulin secretagogues.*
2. Drugs that sensitize tissues (primarily liver and adipose tissue) to the action of insulin named as *insulin sensitizers*.
3. There are drugs that principally affect absorption of glucose therefore retarding the Postprandial hyperglycemia.

❖ **Insulin Secretogogues**

- **Sulfonylureas**

The proposed mechanisms of action of the sulfonylureas include:

a) augmentation of insulin release from pancreatic β cells and

b) potentiating of insulin action on its target cells.

❖ **Meglitinides**

This is another class of secretogauges. They are similar to sulfonylureas in their mechanism of action but lack the sulfonic acid-urea moiety products. Repaglinide is given three times a day 15 minutes before each meal (max. dose.of 16 mg/day); nateglinide is given 60 mg three times a day. The drug may be useful for postprandial hyperglycemia, elderly and in patients with renal impairment. There are less chances of hypoglycemia and useful in patients who have an inconsistent daily schedule with long gaps between meals[18]

Several novel insulin secretagogues have been reported to act by closing the K-ATP channels. The meglitinide derivative mitiglinide (KAD -1229) appears to bind at the benzamide site on SUR113.

❖ **Insulin Sensitizers**

➢ **Biguanides**

Phenformin has been discontinued because of its association with the development of lactic acidosis in patients with coexisting liver or kidney disease. Metformin (1, 1-dimethylbiguanide hydrochloride) was introduced in France in 1957 as an oral agent for therapy of Type II DM, either alone or in combination with sulfonylureas. In 1995 FDA approved its use in the United States but has been used in most of the countries, including India, for over 4 decades. The exact mechanism of action of metformin is not clear but it may reduce hepatic gluconeogenesis, slow down gastrointestinal absorption of glucose and increase uptake by skeletal muscle. It can be used as monotherapy, an adjunct to diet, sulfonylurea's, thiazolidinediones or insulin. Metformin is relatively contraindicated in patients with cardiorespiratory insufficiency, impaired renal function, any state likely to be associated with tissue hypoxia, general anesthesia, use of radiographic contrast media, and age of 70 years. Common side effects of metformin are gastrointestinal symptoms (anorexia nausea vomiting, abdominal discomfort, diarrhea. Lactic acidosis, though uncommon with metformin in contrast to phenformin, is reported in cases with associated risk factors such as renal, hepatic, or cardiorespiratory insufficiency, alcoholism and advanced age 14.

➢ **Thiazolidinediones**

These agents sensitize peripheral tissues to insulin by binding to a nuclear receptor called peroxisome proliferators-activated receptor-gamma (PPARg). Other effects including, increased glucose transporter expression (GLUT I and GLUT 4), decreased free fatty acid levels, decreased hepatic glucose output, and increased differentiation of preadipocytes into adipocytes have also been observed. Troglitazone, was withdrawn because it caused acute liver failure. Rosiglitazone and pioglitazone are used as monotherapy, or in combination with sulfonylurea's, metformin, and insulin. Common side effect is weight gain, especially when the drug is combined with a sulfonylurea or with insulin. The dosage of rosiglitazone is 4-8 mg daily and of pioglitazone 15-45 mg daily. Recently Roziglitazone is withdrawn from India and most other countries due to cardiac safety.

❖ **Inhibitors of Intestinal Carbohydrate Absorption**

- **Alpha-Glucosidase Inhibitors**

Acarbose and miglitol are competitive inhibitors of intestinal brush border alpha-glucosidases, thus delaying the absorption of carbohydrates and reduce postprandial glycemic excursion. Both of these agents are potent inhibitors of glucoamylase, amylase, and sucrase. They are

less effective on isomaltase and are ineffective on trehalase and lactase. The common adverse effect is flatulence. Troublesome diarrhea seen in 3% of cases. The starting dose of acarbose is 25 mg twice daily and can be gradually increased to 100 mg three times daily. A slight rise in hepatic aminotransferases has been noted in clinical trials (5% versus 2% in placebo controls, and particularly with doses greater than 300 mg/d). Miglitol is structurally similar to glucose, is absorbable and is similar to acarbose in terms of its clinical effects. Miglitol should not be used in renal failure since its clearance is impaired in this setting.[19]

- **Incretin Mimetics**

Insulin has been shown to be released more effectively through an oral glucose load than intravenously and this is known as the incretin effect.

Dipeptidyl Peptidase Inhibitors

This class of drugs act slowing breakdown of GLP-1 analogues. These agents works by enhancing the sensitivity of β cells to glucose, which causes enhanced glucose dependent insulin secretion. Many studies using sitagliptin and vildagliptin alone or in combination have shown a positive effect on values of HbA1c.

Phosphodiesterase Inhibitors and other and Approaches

The β - cell expresses several phosphodiesterases (PDEs) that degrade cAMP and so reduce insulin release. Transient inhibition of these enzymes in β- cells, especially isoform PDE-3B, which exerts most influence on glucose induced insulin secretion, could be a possible intervention.[20]

Peroxisome Proliferator Activated Receptor Agonists

Current, thiazolidinediones (pioglitazone and rosiglitazone) exert their "insulin sensitizing" effects largely by stimulating the peroxisome proliferator activated receptor γ. Stimulation of these receptor increase adipogenesis, enhance insulin sensitivity. Additional thiazolidinediones that stimulate PPAR γ are being developed (e.g. rivoglitazone), and non thazolidinedione PPAR γ agonists have been reported.

Other Potentiators of Insulin Action

- **Bromocriptine**

The dopamine D2 receptor agonist bromocriptine used in the treatment of Parkinson disease, galactorrhea and prolactinomas, has long been known to improve insulin sensitivity and glycemic control in Type II DM. Bromocriptine as monotherapy or an adjunct to other antidiabetic agents for up to 1 year has reduced HbA1c by 0.5 – 1.2%, reduced triglyceride, reduced some cardiovascular events, has not caused serious hypoglycaemia.[21]

- **Lipoic Acid, Isoferulic Acid and Angiotensin-Converting Enzyme Inhibitors**

The antioxidant α - lipoic acid, used in some countries to treat diabetic neuropathy, increases insulin sensitivity and improves glycemic control. Isoferulic acid increases expression of GLUT-4 and decreases gluconeogenesis. Modest improvements of insulin sensitivity have been seen during treatment with angiotensin converting enzyme (ACE) inhibitors, possibly because of improved hemodynamics resulting from increased bradykinin.[22]Anti-obesity agents: Several centrally acting appetite suppressing and satiety inducing anti - obesity agents also exert peripheral effects that improve some actions of insulin and assist glycemic control in overweight patients. Sibutramine and Rimonabant: has already been withdrawn because of side effects.[23]

Sodium Glucose Cotransporter 2 Inhibitors

Glucose is filtered through the renal glomeruli and all that has been filtered is reabsorbed in the proximal tubules. Reabsorption is mediated mostly via the sodium glucose co-transporter 2 (SGLT2) systems. Thus, specific inhibition of these transporters reduces hyperglycemia by elimination of excess glucose in the urine. Selective inhibitors of SGLT2 have been developed recently.[24] Possible adverse effects of osmotic diuresis during SGLT2 inhibition include risk of dehydration and electrolyte imbalance, as well as infection in the urinary tract and urogenital region.

Sirtuins

Sirtuins comprise a group of seven enzymes that are nicotinamide adenine-dinucleotide (NAD)-dependent-histone deacetylases and /or ADP ribosyltransferases. Sirtuin SIRT1 is widely expressed in mammalian tissues including liver, muscle and fat, and appears to promote mitochondrial biogenesis and activity in some tissues, increasing thermogenesis and reducing susceptibility to weight gain, diabetes and cardiovascular disease. SIRT1 in pancreatic β- cells may also facilitate insulin secretion. Several small molecule activators of SIRT1 have been studied in animal models.[25]

Management of type I Diabetes Mellitus

Insulin

Insulin is the only therapy available for patients with type I diabetes. Insulin replacement in patients with type I diabetes has been less than optimal because it is not possible to completely reproduce the normal physiologic pattern of insulin secretion into the portal vein.

Four principal types of insulin are available:

(a) Ultra short-acting insulin, with very rapid onset and short duration of action;

(b) Short-acting insulin, with rapid onset of action;

(c) Intermediate-acting insulin; and

(d) Long-acting insulin, with slow onset of action.

Ultra-short-acting and short-acting insulins are dispensed as clear solutions at neutral pH. All other commercial insulins have been specifically modified to obtain more prolonged action.

Rapid and long-acting insulin analogs: Rapid-acting insulin analogs, such as insulin aspart, insulin glulisine and insulin lispro have a faster onset of action, sharper and earlier peak activity and more rapid return to baseline levels than regular human insulin. Given before the evening meal, large doses of regular insulin increase the risk of nocturnal hypoglycemia. These problems are reduced with rapid-acting insulin analogs.[26]Long-acting insulin analogs, detemir and glargine, the first soluble insulin analogs have a prolonged time action profile. Bolus/basal therapy that combines premeal aspart or lispro with glargine or detemir insulin has emerged as the 'gold standard' for intensive injection therapy provided through multiple daily injections (MDI) in adults withType I DM.[27]

Methods of Insulin Administration

A. Insulin Syringes and Needles:

B. Pen devices:

C. Sites for Injection: Any part of the body covered by loose skin can be used as an injection site, including the abdomen, thighs, upper arms, flanks, and upper outer quadrants of the

buttocks. Exercise facilitates insulin absorption when the injection site is adjacent to the exercising muscle.

New and Improved Insulin Delivery Devices

Advances in diabetes technology have helped to improve the outcomes of management of Type I DM in last three decades.

- **Intranasal**
- **Insulin Pumps and Continuous Subcutaneous Insulin Infusion**
- **Continuous Glucose Monitoring (CGM) Systems**

❖ **Other Modes of Therapy in Type I DM.**

- **Amylin Analogues**
- **Pancreatic and Islet Transplantation**
- **Immunotherapy**

❖ **Novel Drugs**

1. Alogliptin (Nesina, Kazano, Oseni): Approved January 2013

On January 25, 2013, Takeda Pharmaceutical received approval for alogliptin, a type II diabetes drug. Alogliptin is a dipeptidyl peptidase IV (DPP-4) inhibitor that stimulates the release of insulin by preventing GLP-1, a compound that helps to lower blood sugar, from breaking down.

2. Invokana: Approved March 2013

Invokana (canagliflozain) from Janssen Pharmaceuticals is the first in a new class of type II diabetes drugs that was **FDA approved** in March 2013. Invokana is a **sodium-glucose co-transporter 2 (SGLT2)** inhibitor that blocks the reabsorption of glucose (blood sugar) by the kidneys and increases glucose excretion in the urine. This oral diabetes treatment is indicated to improve blood sugar control in conjunction with diet and exercise in patients with type II diabetes.

3. Farxiga: Approved January 2014

In January 2014, the U.S. Food and Drug Administration (FDA) approved **Farxiga (**dapagliflozin) tablets to improve glycemic (sugar) control, along with diet and exercise, in adults with type II diabetes. Like Invokana, Farxiga is also a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Farxiga's effectiveness was shown in 16 clinical trials involving more than 9,400 patients.

4. Tanzeum: Approved April 2014

GSK's **Tanzeum** (albiglutide), approved in April 2014, is classified as a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a hormone that helps normalize blood sugar levels in patients with type II diabetes. Tanzeum binds to GLP-1 to stimulate the release of glucose-dependent insulin, while blocking release of sugar-boosting glucagon from the pancreas. Tanzeum is given by subcutaneous (under the skin) injection, and, as with most diabetes treatments, is to be used alongside diet and exercise. The safety and effectiveness of Tanzeum was shown in eight clinical trials involving over 2,000 participants with type II diabetes.

5. Jardiance: Approved May 2014

In May 2014, the **FDA approved** the third SGLT blocker to enter the U.S. market, Jardiance (empagliflozin). In seven type II diabetes clinical trials with about 4,500 people, Boehringer Ingelheim's **Jardiance** improved hemoglobin A1c levels compared to placebo. Jardiance can also be used with metformin, sulfonylureas, pioglitazone, and insulin.

6. Afrezza: Approved June 2014

Afrezza (insulin human) Inhalation Powder was approved by the FDA in June 2014. Afrezza is an ultra-rapid-acting inhaled insulin that is administered with meals to improve glycemic control in adult diabetics. In clinical trials, Afrezza was evaluated in 24-week studies in both type I and type II diabetic patients. In 1,026 type I patients also using long-acting insulin, Afrezza effectiveness to lower blood sugar (A1c) provided less A1c reduction than insulin aspart (an injectable fast-acting insulin), and the difference was statistically significant. In 1991 type II patients also using oral antidiabetic agents, inhaled Afrezza did significantly lower A1c compared to a placebo group (also using oral antidiabetics) in a 24-week study. Afrezza, because it is inhaled and not injected, may cause the serious side effect of bronchospasm in patients with asthma or chronic obstructive pulmonary disease (COPD), and should not be used in these patients. The most common adverse reactions associated with Afrezza in clinical trials were hypoglycemia (low blood sugar), cough, and throat pain or irritation.

Herbs used in the treatment of Diabetes

It has been estimated that more than 400 traditional plants or plant-derived products have been used for the management of type II diabetes across geographically and about 800 plants have anti-diabetic potential. Plants have their chemical compounds which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having antidiabetic effect. Herbalism is becoming focusing point due to research on herbs and their use in treatment of diabetes and its prevention The scientific study of traditional medicines, concerned medicinal plants are thus of great importance.

Table 2: List of some of the important Antidiabetic plants with their family

Name of plant	Family	Part used	Acivity found
Alangium lamarckii	Alangiaceae	Leaves	Antidiabetic activity
Albizia odoratissima	Mimosaceae	Bark	Antidiabetic activity
Axonopus compressus	Poaceae	Leaves	Antidiabetic activity
Acorus calamus	Leguminosae	Seeds	Antidiabetic activity
Aloe vera	Araceae	Radix	Antidiabetic activity
Azadirachta indica	Meliaceae	Leaves, seeds	Antidiabetic activity
Bauhinia forficate	Fabaceae	Leaves	Antidiabetic activity
Berberis vulgaris	Berberidaceae	Root	Antidiabetic activity
Brassssica juncea	Cruciferae	Seed	Antidiabetic activity
Beta vulgaris	Chenopodiaceae	Root	Antidiabetic activity
Bixa orellana	Bixaceae	Leaves	Antidiabetic activity
Caesalpinia digyna	Fabaceae	Root	Antidiabetic activity
Catharanthus roseus	Apocynaceae	Leaf	Antidiabetic activity
Costus specious	Costaceae	Root	Antidiabetic activity
Curcuma longa	Zingiberaceae	Rhizome	Antidiabetic activity
Dendrobium chrysotoxum	Orchidaceae	Stem	Antidiabetic activity
Dolichandrone falcata Seem.	Bignoniaceae	Leaf	Antidiabetic activity
Emblica officinalis	Euphorbiaceae	Fruit	Antidiabetic activity
Eucommia ulmoides **Oliv.**	Eucommiaceae	Leaf	Antidiabetic activity
Eugenia jambolona	Myrtaceae	Seeds	Antidiabetic activity
Ficus bengalensis	Moraceae	Root, Stem	Antidiabetic activity
Ficus carica	Moraceae	Leaves	Antidiabetic activity
Flacourtia jangomas **Raeusch**	Flacourtiaceae	Leaves	Antidiabetic activity
Gardenia taitensis **A. P. de Candolle**	Rubiaceae	Leaves	Antidiabetic activity
Gymnema Sylvestre	Asclepiadaceae	Whole plant	Antidiabetic activity
Holoptelea integrifolia **(Roxb.)**	Ulmaceae	Stem	Antidiabetic activity
Hypericum perforatum L.	Hypericaceae	Leaves	Antidiabetic activity
Hedychium spicatum	Zingiberaceae	Rhizome	Antidiabetic activity
Juglans regia L.	Juglandaceae	Leaves	Antidiabetic activity
Juniperus chinensis	Cupressaceae	Fruit	Antidiabetic activity
Lagerstroemia speciosa **(L.) Pers**	Lythraceae	Leaves	Antidiabetic activity
Linum usitatisumum	Linaceae	Seeds	Antidiabetic activity
Memecylon umbellatum **Burm.F**	Melastomataceae	Leaves	Antidiabetic activity
Mimosa pudica L.	Mimosaceae	Leaves	Antidiabetic activity
Murraya koenigii	Rutaceae	Leaves	Antidiabetic activity
Myrcia uniflora	Myricaceae	Leaves	Antidiabetic activity
Ocimum sanctum	Lamiaceae	Leaves	Antidiabetic acitvity
Olea europaea	Oleaceae	Leaves	Antidiabetic acivity
Paeonia lactiflora	Paeoniaceae	Roots	Antidiabetic activity
Raphanus sativus	Brassicaceae	Root	Antidiabetic activity
Solanum trilobatum	Solanaceae	Leaves	Antidiabetic activity
Sonneratia alba	Sonneratiaceae	Leaves	Antidiabetic activity
Spinacia oleracea	Chenopodiaceae	Leaves	Antidiabetic activity
Symplocos cochinchinensis	Symplocaceae	Leaves	Antidiabetic activity
Tridax procumbens	Asteraceae	Whole plant	Antidiabetic activity
Urtica dioica	Urticaceae	Leaves	Antidiabetic activity
Withania somnifera	Solanaceae	Root	Antidiabetic activity
Zizyphus sativa	Rhamnaceae	Leaves	Antidiabetic activity

Conclusion

The global costs of diabetes and its consequences are large and will substantially increase by 2030. Even if countries meet the international targets, the global economic burden will not decrease. Herbal Drugs can play an effective role in lowering the global economic burden as these are cost effective and by implication of recent advanced technologies like Nanotechnology can increase the higher therapeutic index of Herbal Drugs.

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