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DIABETES MELLITUS: ROLE OF BOTANICAL PHARMACY

[1,*] Ravindra B. Malabadi, [2]Kiran P. Kolkar, [3,4]Manohara Acharya, [5]Divakar MS, [1]Raju K. Chalannavar

[1]Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India.
[2]Department of Botany, Karnatak Science College, Dharwad-580003, Karnataka State, India.
[3]Department of Applied Botany, Mangalore University, Mangalagangotri, Mangaluru-574199, Karnataka, India.
[4]Department of Botany, Canara College, Mangaluru-575003, Karnataka, India.
[5]Biotechnology Unit, Department of Biosciences, Mangalore University, Mangalagangotri, Mangaluru-574 199, Karnataka, India.

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ABSTRACT

Diabetes mellitus (DM) is a chronic endocrine disorder which is characterized by high blood glucose levels that can interfere with carbohydrate, protein, and fat metabolism. Diabetic patients defects in insulin secretion or insulin action or both. Effective treatment of diabetes is still a major challenge in spite of approved drugs such as biguanides, metformin, Januvia (Sitagliptin phosphate tablets), thiazolidinediones, sulfonylureas, a-glucoside inhibitors, thiazolidinediones, and insulin for the diabetes. However, all these pharmaceutical drugs have serious harmful side effects. Traditional plants are reported to have significant antidiabetic properties with no harmful side effects. Ayurveda offers comprehensive safe and effective approaches to manage diabetic disorder. Ayurvedic treatment is effective to reduce the side effects and to improve general well-being of the diabetic patient. This review paper provides useful information about the clinically proven medicinal plants for the treatment of type-2 diabetes.

Keywords: Ayurveda, diabetes, ethanobotany, herbal medicine, Insulin, India, Metformin

INTRODUCTION

India is the largest producer of medicinal plants and well known for its practice of traditional medicine Ayurveda and ethno pharmacology (1-20). India is rich with a flora of indigenous medicinal plants that have been used for centuries in traditional Indian medicine to treat diabetes (1-9). Use of plants as a source of medicine has been an ancient practice and is an important component of the health care system in India (1-10). Plants are always the key source of drug or treatment strategy in different traditional medicinal systems (1-26). The Indian subcontinent is a vast repository of medicinal plants that are used in the traditional medical treatments (1-11). The alternative medicines in the traditional systems are derived from herbs, and herbal drugs were produced from medicinal plants (1-20). Therefore, medicinal plants are considered as a vital source of new drug. In India, approximately 80% of modern drugs are discovered from natural resources and number of other synthetic analogues have been prepared from prototype compounds isolated from plants (1-26).

In India, about 70 percent of rural population depends on the traditional Ayurvedic system of medicine (1-15). Ayurveda is a comprehensive scientific medicinal system indigenous to India. The term Ayurveda means 'knowledge of life', which comprises two Sanskrit words, Ayu (life) and Veda (knowledge or science) (1-10). Ayurveda is also called as the "science of longevity" because it offers a complete system to live a long healthy life. The primary goal of Ayurveda is to maintain equilibrium between the 5 basic elements (Panchamahabhutas) of earth, water, fire, air, and ether or vacuum within oneself through the theory of the 3 life forces or doshas (48).

Ayurveda offers programs to rejuvenate the body through diet and nutrition (1-15). Ayurveda can also be integrated in care for diabetes (1-26). Ayurveda offers outstanding drugs and treatments which can be easily included along with the main stream diabetic medicines. Ayurvedic treatment is effective to reduce the side effects and to improve general well-being of the diabetic patient (1-25).

AYUSH practitioners however have a much wider presence in rural and remote areas (1-8). Most healers/practitioners of the traditional systems of medicine prepare formulations by their own recipes and dispense to the diabetic patients (1-20). In recent years, many people are choosing to plant based medicines or products to improve their health conditions or as curative substance either alone or in combination with others. More than 70 percent of people in developing countries cannot afford the most basic medical procedures, drugs, and vaccines (1-9). In recent years, a huge resurgence of the use of herbal product due to the side effects of modern drugs, failure of modern therapies against chronic diseases, and microbial resistance. It is estimated that nearly 75% of the plant based therapeutic entities used worldwide were included from traditional/folk medicine (1-20).

This review paper highlights the medicinal plants with antidiabetic activity. Advancement in diabetes research has resulted in the development of several pharmaceutical drugs such as biguanides, metformin, Januvia (Sitagliptin phosphate tablets), thiazolidinediones, sulfonylureas, a-glucoside inhibitors, and insulin. All these drugs showed hypoglycemic activities, they are often associated with several complications such as nephrological disorders, fatigue, upset stomach, diarrhea, etc and many side effects. Therefore, many medicinal plants with hypoglycemic properties have been used individually or in formulations for the treatment of type-2 diabetes based on clinical and laboratory evidence. A list of medicinal plants with proven anti-diabetic activity of herbal drugs used in the treatment of type-2 diabetes is compiled (Table-1).

Diabetes

Diabetes mellitus is a chronic metabolic disorder of carbohydrate, protein and fat resulted in the increased number of diabetic patients throughout the world (27-34, 37-40). Diabetes

***Corresponding Author: Ravindra B. Malabadi,**
1Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India.

mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. In India, with current population of 1.4 billion (As of 2022), approximately 100 million people have been affected by the diabetes with the life threatening complications which makes it the second most affected in the world, after China. One in six people (17%) in the world with diabetes is from India (37-40). Therefore**, India is known as the diabetes capital of the world** and **this diabetic condition in India has been shifted from endemic form to pandemic** (37-40). These data showed that the number of patients with diabetes is increasing at an alarming rate and have come to represent a challenge for human health. In Western countries, 90% of type-1 diabetic condition is more common in childhood and adult populations (Between the age group of 5 to 25) where as in India type-2 diabetic cases are very high in number (90%) in elderly people (between the age group of 45-70) (37-40). Diabetes mellitus has a significant adverse effect on quality of life in terms of social, psychological and physical health (37-40). Diabetes mellitus is characterized by chronic hyperglycemia condition (high sugar levels) defects in insulin secretion or insulin action or both (27-36). Hyperglycemia is a complication of diabetes. It occurs when the blood sugar level is above normal values: above 7 mmol/L, on an empty stomach or before a meal.

Another common name of diabetes is called as the **Sweet urine disease.** In India, a traditional herbal practioners identify a person suffering from Madhumeha (Diabetes) passes sweet urine and exhibits sweetness all over the body (27-34). They have also recorded their observation that if too many ants swarm around the spot of urine, then the person have symptoms of diabetes mellitus (27-34, 37-40). Hence a person suffering from diabetes has an increased urinary output, increase thirst and ketonemia due to abnormalities of carbohydrate, protein and fat metabolism (27-34, 37-40).

Ketones form in the diabetic patient body when body starts using fat instead of carbohydrates to create energy. When the body does not have enough insulin to move glucose (sugar) from the blood to the cells, the body uses fat to create energy. When fat is broken down, ketones are formed and can then accumulate in the body (37-40). High ketone levels (ketones in the blood) are toxic to diabetic patient body. The accumulation of ketones in the blood is called ketoacidosis which is one of the symptoms of diabetic person. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total lack of insulin, patients are given insulin injections (37-40). Currently, the main and effective treatment for diabetes is the use of insulin and hypoglycemic drugs, but these compounds also have many adverse side effects.

Types of Diabetes

On the basis of etiology, there are two types of diabetes mellitus; one is called as Type-1 diabetes (insulin dependent diabetes). The second one is called as Type-2 diabetes (non-insulin dependent diabetes) (37-40).

Type-1 diabetes

Type-1 diabetes is also known as insulin dependent diabetes. Insulin is a hormone produced by the pancreas. It helps the body to use glucose and control its level in the blood. Because people with type 1 diabetes do not produce insulin, they depend on insulin injections for survival (27-34). The amount of insulin produced in a normal human is about 40 units. Normal human pancrease contains about 8-10mg of insulin. Insulin is not suitable for oral administration due to inactivation by digestive enzymes, and 80% of exerted insulin is normally degraded in the liver and kidneys. The type-1 diabetes occurs in childhood and adulthood (between the age of 5 years to 25 years) mainly due to destruction of pancreatic β- cell islets through autoimmune mediated resulting in insulin deficiency. The patient suffering from type-1 diabetes unable to synthesize his own insulin. Therefore, external insulin injection has been given to Type-1 diabetic patient to control the blood glucose levels. In Western countries, 90% of Type-1 diabetic cases have been recorded. Genetic defects of β-cell function or insulin action is the main reason for the occurrence of Type-1 diabetes. In India, total no of Type-1 diabetic cases is less than 25%. Therefore, Type-1 diabetic patient family history is very important in the identification of type-1 diabetes. Type-1 diabetes is also associated with life style and genetic factors such as genetic syndromes, chromosomal and mitochondrial DNA mutations (27-34, 37-40).

Type-2 diabetes

Type-2 diabetes is also called as non-insulin diabetes. Patients suffering from Type -2 diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and oral medication. The type-2 diabetes is very common in India between the age group of 45-65 (27-34, 37-42). Type 2 diabetes mellitus is a type of metabolic disease caused by metabolic disorders in the endocrine system and characterized by hyperglycemia (41-42). Insufficient insulin secretion and insulin resistance are the basic pathologic characteristics of type-2 diabetes. Another major problem is that additionally, it is estimated that approximately half of all adult patients worldwide have not been diagnosed as of 2022. In addition, type-2 diabetes accounts for approximately 95% of the total population of diabetes, which leads to significant losses for human and economic health. Type-2 diabetes is a chronic disease that can cause a series of complications that can lead to death (41-42). At present, the treatment of type-2 diabetes mainly depends on lifestyle intervention (such as nutrition therapy and physical activity), oral medication (such as biguanides, sulfonylureas, and a-glucoside inhibitors), injected drugs (such as insulin and glucagon like peptide-1- amide [GLP-1] agonists), surgical treatment, and complementary and alternative treatment (41, 42).

Symptoms of diabetes

Diabetes has also caused morbidity and mortality due to symptoms of retinopathy (Eye disease), neuropathy (nerve disease), nephropathy (kidney disease), diabetes ketoacidosis (DKA), fatigue or lack of energy, dehydration, kidney failure, wound healing problem, dry skin conditions, appearance of dark spots on skin, darkened patches of skin called acanthosis nigricans, increased urinary output, loss of sexual desire, low sperm count, premature ejaculation, and physical weakness, Erectile dysfunction (ED) generally known as male impotency is a major health disorder affecting reproductive organ in male partner, appearance of white spots on nails, extreme hunger (35), Irritability and mood changes, rapid weight loss, blurred vision, frequent infections of skin, recurring skin, gum, or urinary tract infections, drowsiness, trouble getting or maintaining an erection, slow healing of cuts and or bruises, Tingling or numbness in the legs, feet, or fingers, Nausea, vomiting, or stomach pains may accompany some of the symptoms in the abrupt onset of insulin-dependent diabetes, feel very tired, heart attack, stroke, and cardiovascular diseases (27-34, 37-40).

Causes of diabetes

According to the health experts, the main reason for an increasing type-2 diabetic conditions in India are rapid rise in unhealthy busy life style, stress conditions, lack of exercise, bad food habits, there is no time gap difference between dinner and bed time,

many people are hesitant to diagnose for diabetes, sometimes long term use of medications such as dexamethasone, L-asparaginase, glucocorticoids, cyclosporin or tacrolimus, olanzapine, risperidol, quetiapine, and ziprasidone, sugar levels are not properly maintained and monitered particularly in urban areas. Hyperglycemia (high sugar levels) condition leads to the generation of Reactive Oxygen Species (ROS) which causes lipid peroxidation and membrane damage leading to cataract, neuropathy and nephropathy. Further production of free radicals is also involved in the pathogenesis of various types of diseases including diabetes. Therefore, natural plant antioxidants such as tannins, flavonoids, alkaloids, vitamin C, E protects β-cell function from the oxidation, thus play an important role in diabetes and prevent diabetes induced ROS formation (27-36).

Food is the major source for serving the nutritional needs, but with growing modernization some traditional methods are being given up. Hence, the modern food habits are affecting the balanced nutrition. There is an ever widening gap in nutrient intake due to which normal life is no longer normal. However, affluence of working population with changing lifestyles and reducing affordability of sick care, in terms of time and money involved, are some of the forces that are presently driving people towards thinking about their wellness.

Medication and diagnosis of diabetes

Diabetes can be confirmed by the measurement of a marked elevation of blood glucose level. Diagnosis may require continued observation of 8 hour fasting glucose level and after meal, the glucose levels should be observed and recorded. Now a day's blood glucose levels can be measured using glucometer (37-40). The use of Aldose reductase inhibitors and α- glucosidase inhibitors has been reported in the treatment of diabetic complications (27-34). The plant (Galega officinalis) derived Metformin with Januvia (Sitagliptin phosphate tablets) has been prescribed as a medication in the treatment of type-2 diabetic condition on the basis of consultation of family doctor or physician (27-34). Any medication should not be taken without consultation of physician. Januvia (Sitagliptin phosphate tablets) is an orally-active potent and highly selective inhibitor of dipeptidyl pdptidase-4 (DPP-4) enzyme for the treatment of type-2 diabetes. Sitagliptin is a diabetes drug that works by increasing levels of natural substances called incretins. Incretins helped to control blood sugar by increasing insulin release, especially after a meal. They also decrease the amount of sugar liver makes. Insulin has been recommended as the best treatment for the type-1 diabetic disorder. Measurement of specific autoantibody markers such as islet cell antibody (ICA), GAD, IA2, IAA, HbA1c may be helpful for the diagnosis of diabetes mellitus.

For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long lived proteins, such as elastin, laminin, collagen are the major targets of free radicals. These proteins are modified to form glycoproteins due to hyperglycemia. Free radicals are capable of damaging cellular molecules, DNA, proteins and lipids leading to altered cellular functions (27-34, 37-40). During diabetes, lipoproteins are oxidized by free radicals. Furthermore multiple abnormalities of lipoprotein metabolism in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) in diabetes. Lipid peroxidation is enhanced due to increased oxidative stress in diabetic condition. Apart from this, advanced glycation end products (AGEs) are formed by non-enzymatic glycosylation of proteins, AGEs (27-34, 37-40).

Warning and side effects

Both metformin and JANUVIA (Sitagliptin phosphate tablets) were used for the treatment of type-2 diabetes. However, JANUVIA (Sitagliptin phosphate tablets) can cause serious side effects, including pancreatitis, which may be severe and lead to death. Therefore, before taking any medication, family Doctor or physician should be consulted for the diabetes. Further FDA has also warned about the side effects of JANUVIA.

Metformin (**1-1-Dimethyl-biguanide**) ($C_4H_{11}N_5$) is commonly referred as the Glyciphage (Glucose destroyer) which has been known for centuries as a herbal medicine in the treatment of type-2-diabetes mellitus (34). Metformin (1-1-Dimethyl-biguanide) ($C_4H_{11}N_5$) is a synthetic biguanide, orally effective and insulin sensitizing anti-diabetic drug for the type 2 diabetes mellitus. Metformin (Glucophage or Glyciphage = Glucose eater) is not an insulin but is considered an insulin sensitizer (34). The dosage of metformin is usually 1-3 pills per day at different sizes of 500 mg, 850 mg, or 1000 mg, taken with meals in order to reduce adverse gastrointestinal side effects. Gastrointestinal effects occur in up to 50% of patients using metformin (34). Metformin could cause constipation, bloating, diarrhea, nausea, abdominal pain, vomiting, flatulence, anorexia, and dyspepsia, but these symptoms are almost always transient and resolved within a few days, especially when metformin is taken with food or in a gradual titration. Gastrointestinal effects are mainly related to metformin dosage which is usually changed or when taken in combination with other drugs (34). Gastrointestinal upset can cause severe discomfort and it is the most common when metformin is first administered, or when the dose is increased (34). Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B12. Higher doses and prolonged use of metformin are associated with increased incidence of vitamin B12 deficiency (34). The most serious potential adverse side effect of metformin is lactic acidosis (34). This complication is rare, and the vast majority of these cases seem to be related to conditions such as impaired liver or kidney function, rather than to the metformin itself. Metformin is not approved for use in those with severe kidney disease, but may still be used at lower doses in those with kidney problem (34). The most common symptoms following an overdose of metformin include constipation, vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and rarely, hypoglycemia or hyperglycemia (34).

Diabetic older (60 to 70 age group) patients with long term medication of higher dose (1000mg) of metformin suffers from constipation. Constipation leading to three bowel movements a week, stools are dry, hard and/or lumpy, stools are difficult or painful to pass, stomach ache or cramps, and feel bloated and nauseous. Constipation happens because colon absorbs too much water from waste (stool/poop), which dries out the stool making it hard in consistency and difficult to push out of the body. Food normally moves through the digestive tract, nutrients are absorbed. The partially digested food (waste) that remains moves from the small intestine to the large intestine, also called the colon. The colon absorbs water from this waste, which creates a solid matter called stool. In case of diabetic patients with constipation, food may move too slowly through the digestive tract. This gives the colon more time too much time to absorb water from the waste. The stool becomes dry, hard, and difficult to push out.

The most important classes of antidiabetic oral medicines include biguanides, such as metformin, sulfonylureas, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 inhibitors, sodium glucose cotransporter (SGLT2) inhibitors and α-glucosidase inhibitors. The other glucosidase inhibitors such as acarbose, miglitol and voglibose are used. These inhibit degradation of carbohydrates thereby reducing the glucose absorption by the cells. To enhance glucose uptake by peripheral cells biguanide such as metformine is used. Sulphonylureas like glibenclamide is insulinotropic and works as

secretogogue for pancreatic cells. However, all these oral medications have side effects (27-36).

Diabetes: Measurement of blood glucose levels

The recommended blood sugar level ranges in countries around the world are very similar. However, there are two different units of measurement that are used when referring to blood sugars : millimoles per litre (mmol/L) and milligrams per decilitre (mg/dL). The mmol/L measurement is used in Canada, England, Australia and China. On the other hand mg/dL is used in India, United States, France, Japan, and Israel. To convert mmol/L to mg/dl, simply multiply by 18. For example, a blood sugar level of 5.0 mmol/L would mean a level of 90 mg/dL (5 x 18 = 90).

A blood sugar level less than 140 mg/dL (7.8 mmol/L) is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours indicates diabetes. A reading between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes. Normal blood glucose levels can be measured when someone fasts, eats, or after they have eaten. A normal blood glucose level for adults, without diabetes, who have not eaten for at least eight hours (fasting) is less than 100 mg/dL. A normal blood glucose level for adults, without diabetes, two hours after eating is 90 to 110 mg/dL.

Blood sugar levels are considered high if they are over 130 mg/dL before a meal or 180 mg/dL within one to two hours after a meal. Many people will not start to experience symptoms from high blood sugar until their levels are at 250 mg/dL or higher. The highest blood sugar level that is considered safe will depend on the person and whether they have diabetes, but will typically be between 160 to 240 mg/dL (37-40).

Diabetes: Role of Botanical Pharmacy

There are some medicinal plants believed to treat diabetes, and scientific studies have reported certain medicinal plants do contain antidiabetic properties, such as improved insulin sensitivity and hypoglycemic activities (Table-1) (41- 49). It is often associated with their high level of phenolic compounds, flavonoids, terpenoids, alkaloids, and glycosides, which can improve insulin secretions as well as control blood glucose (41, 43). Evidence-based research in Ayurveda is receiving larger acceptance in India and abroad (1-26). Furthermore, herbal medicines are very chief, easily available, and also affordable for poor people, and there are no side effects too (1-24). Ayurvedic and other Indian traditional medicine in clinical practice will helpful to promote the health of the people who are unable to access the modern medicine properly (1-11). Traditionally, it is known fact that plants naturally contain healing properties for various ailments, have been used for generations, and play an important role in leading modern medicine (Table-1) (41, 45, 48). Deregulation of eating behaviour is common in industrialized countries. Patients with type 2 diabetes are likely to have high postprandial blood glucose levels, especially after consuming carbohydrates (41-50). Elevated blood glucose results from the breakdown of carbohydrates by the digestive enzymes, alpha-amylase and alpha-glucosidase and the reduced ability of cells to take in glucose from the blood (45). Herbal formulations are favoured over synthetic drugs to reduce the ill-effects of diabetes and its secondary complications due to lesser side effects and also being cost effective (41-50). The medicinal plants with antidiabetic activity has been listed in the table-1.

CONCLUSION

Diabetes is a chronic metabolic disease reaching an epidemic proportion in many parts of the world associated with high rates of morbidity and mortality. The chronic nature of diabetes mellitus and its complications motivate patients to use alternative medicine to treat their condition. Complementary and Alternative Medicine (CAM) is widely used throughout the world especially by patients with chronic diseases such as type 2 diabetes mellitus. Herbal medicine is superior in its holistic quality, which can treat type-2 diabetes through multiple targets, and is a good complementary and alternative treatment for type-2 diabetes. Herbal medicine is mainly used to treat type-2 diabetes through its anti-inflammatory, anti-oxidation, blood lipid regulation, and anti-glucose properties. Therefore, this review is aimed at opening up new vistas in realizing the therapeutic potential of Ayurveda in treatment of diabetes.

One of the major problems with this herbal formulation is that the active ingredients are not well defined. Herbs, especially some herbal formulas, contain a variety of ingredients, and it is difficult to accurately identify the active ingredients and toxic ingredients. Most of the above studies are animal experiments. However, some of the medicinal plants demonstrated antidiabetic activity in animal models only and failed to show antidiabetic activity in the human clinical trials. Every year literature on the antidiabetic plants is go on increasing rapidly on the basis of animal study experiments but data on the human clinical experiments is lacking. Therefore, polyherbal combinations have been introduced for the human clinical studies. This might solve the current problems of animal and human clinical trial experiments. Large-scale, multicenter clinical studies still lack reliable and detailed information. Hence herbal drugs may be an emerging alternative of synthetic drugs to curing diabetes mellitus.

Table: 1. Medicinal plants with Antidiabetic activity in the management of type-2 diabetes

SL. No	Plant name	Family	Pharmaceutical activity
1	Gymnema sylvestre (Gurmar)	Asclepiadaceae	Leaf, stem, root Madhunashini or sugar destroyer (Gymnemic acids)
2	Costus speciosus (Insulin plant)	Zingiberaceae	Rhizome Antidiabetic activity (Diosgenin, curcumin, curcuminoids)
3	Momordica charantia (Bitter melon or Gourd) (Hagalakai)	*Cucurbitaceae*	Fruits (Glycosides, saponins, biguanide, alkaloids)
4	Trigonella foenum-graecum (Fenugreek) (Methi)	Fabaceae	Seeds, Leaf Antidiabetic (Diosgenin saponin, biguanide & 4-hydroxyisoleucine)
5	Murraya koenigii (Curry leaves, Methi)	Rutaceae	Leaf (Antidiabetic activity) Biguanide related compounds (BRC)
6	Allium sativum (Garlic)	Amaryllidaceae	Fruits (Antidiabetic activity) Biguanide related compounds (BRC)
7	Tinospora cordifolia (Guduchi or Giloy) (Amruthaballi)	Menispermaceae	Leaf, stem, root (Antidiabetic) Isoquinoline alkaloid (Glycosides, flavonoids, saponins)
8	Azadirachta indica (Neem tree)	Meliacaea	Leaf (Antidiabetic, antiviral)
9	Triphala Emblica officinalis (Amalaki), Terminalia bellerica (Bibhitaki), and	Euphorbiaceae Combretaceae	Fruits mixture (Antidiabetic and antiviral)

	Terminalia chebula (Haritaki),	Combretaceae	(Ellagitannins and Gallotannins)
10	Glycyrrhiza glabra (Liquorice)	Leguminosae	Root: Antidiabetic activity
11	Lantana camara	Verbenaceae	Leaves: Antidiabetic
12	Phyllanthus amarus	Phyllanthaceae	Whole plant: Antidiabetic
13	Andrographis paniculata	Acanthaceae	Antidiabetic
14	Pongamia pinnata	Fabaceae	Antidiabetic
15	Prunus amygdalus	Rosaceae	Seed: Antidiabetic
16	Sarcopoterium spinosum	Rosaceae	Root: Antidiabetic
17	Swertia punicea Swertia chirata	Gentianaceae	Whole plant: Antidiabetic
18	Vernonia amygdalina	Asteraceae	Aerial part/seed :Antidiabetic
19	Petrocarpus marsupium	Leguminaceae	Dried juice of plant: Antidiabeti

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