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Natural Diabetes Treatment: An Overview

Darakhshan Afreen Shaikh[1], Rashmi Patil[2]

Oriental College of Pharmacy, Sanpada, Navi Mumbai, Mumbai University, Maharashtra, India

Abstract: ***Diabetes is a metabolic disorder characterized by elevated blood glucose resulting from increased hepatic glucose, inadequate insulin secretion and impaired insulin action. Insulin is secreted by beta cells of islets of Langerhans of pancreas. Diabetes is also termed as hyperglycaemia that is elevated blood glucose. Antihyperglycemics treat diabetes by lowering blood glucose level. Hyperglycaemia results in significant morbidity and mortality. Diabetes is associated with various complications like peripheral neuropathy, nephropathy, retinopathy, artery disease, etc. One of the etiologic implicated in the development of diabetes and its complications is the damage induced by free radicals and hence an antidiabetic compound with antioxidant properties would be more beneficial, hence herbs having antioxidant properties are also included. Various herbs are classified on the basis of their parts used in the treatment of diabetes, along with their chemical constituents.***

Keywords: Hyperglycaemia**,** diabetes mellitus, diabetes insipidus, neuropathy, peripheral vascular disease

1. Introduction

Diabetes is a chronic disorder characterized by metabolic diseases in which the person has high blood glucose level, either because of inadequate insulin production or because the body's cells do not respond properly to insulin, or both. It is disorder of carbohydrate, fat and protein metabolism [1]. It is characterized by increased fasting and postprandial blood sugar levels. Diabetes is caused due to oxidative stress and increase in reactive oxygen species. Untreated diabetes leads to ketoacidosis i.e. accumulation of ketones and acids in blood. Diabetes mellitus occurs especially due to lifestyle changes, sedentary lifestyle, less physical activity. [2] Nutrient poor food, etc. The global prevalence of diabetes might increase by 55% during 2013-2035. Poor control of blood sugar levels in diabetic patients lead to heart and blood vessel diseases, kidney failure, nerve damage, eye problems, etc. Diabetes may cause diseases of blood vessels, coronary diseases, and peripheral arterial diseases. There is tremendous increase in rates of diabetes in low and middle-income countries.

1.1 Types of diabetes

Diabetes mellitus: Diabetes mellitus is further classified as Type -I and Type – II

Type -I diabetes- Type -I diabetes occurs due to lack of functional beta cells .It is also known as juvenile diabetes because it usually appears during childhood or adolescence. Blood sugar cannot get into cells without insulin and builds up in the bloodstream. Type1 diabetes is observed in 10% of cases and it can be controlled by administering insulin injections to prevent hyperglycaemia. Type -I is autoimmune disorder and generally this type is less common. [21]

Type -II diabetes- In type II diabetes body does not produce enough insulin or cells do not respond to insulin properly. In this type pancreas retain some beta cells functional, but effective insulin response is inadequate for the normal glucose level, which leads to hyperglycaemia. It is also called as non-insulin dependent diabetes mellitus. It occurs in middle or older age. Metformin is the medication recommended mostly in this type of diabetes. Patients suffering from Type - II diabetes have shorter life expectancy. Type - II diabetes is mostly associated with hypertension and dyslipidaemia. [20]

Diabetes insipidus: Diabetes insipidus is a rare condition that occurs when your kidneys do not conserve water properly. It occurs due to lack of Antidiuretic hormone production or its use which leads to polydipsia which is intense thirst or polyuria (excretion of large amounts of urine).

Diabetes insipidus is of four types:

1) **Central Diabetes Insipidus**-There is no enough Antidiuretic hormone production in this type.
2) **Nephrogenic Diabetes Insipidus**-Kidneys do not respond normally to Antidiuretic hormone in this type.
3) **Dipsogenic Diabetes Insipidus-** It is caused by a problem with sense of thirst, it causes to be abnormally thirsty and also produces more urine [2].
4) **Gestational Diabetes Insipidus-** It occurs only during pregnancy.

Gestational diabetes: Gestational diabetes can occur at any stage of pregnancy but usually in second or third trimester [21], when body of pregnant women cannot produce enough insulin or resist insulin. Gestational diabetes affects 4% of pregnancies, especially common during the last three months of pregnancy. A woman is diagnosed with gestational diabetes when glucose intolerance continues beyond 24 to 28 weeks of gestation. Pre-eclampsia, preterm labour and dry mouth are some of the symptoms of gestational diabetes. It is associated with foetal and maternal morbidity. [1]

Symptoms of diabetes: Frequent urination, excessive thirst, extreme hunger, dramatic weight loss, irritability, weakness and fatigue, itchy or dry skin, dry mouth, nausea and vomiting, blurry vision, slow healing sores, frequent infections.[4]

Causes of diabetes: Genetics, hormonal diseases ,chemical toxicity, exposure to viruses and environmental factors[3] , age, amputation, abnormal function of pancreas, unhealthy eating habits, overweight, excessive alcohol consumption, stress, work load, nutritional deficiencies, smoking, lack of

exercise or physical inactivity[2] ,damage or removal of the pancreas, hereditary predisposition.

Complications associated with diabetes: The long term complications of diabetes may be divided into two large groups:

1) Macrovascular: Pathology of large and medium-sized vessels; includes Coronary Heart diseases, Stroke, Peripheral vascular disease [5].
2) Microvascular: Vascular pathology of small vessels and include Neuropathy, nephropathy, retinopathy.

Precautions to avoid diabetes: Follow low calorie diet, loose excess body fat, increase physical exercise, avoid stress, sleep well optimize vitamin D levels , quit smoking , avoid use of medicines like cortisone, control your blood pressure, do not skip meals, regular check-up of blood glucose, blood pressure and cholesterol levels, limit fast food and sugar , proper fitting and cushioned footwear, clean and dry socks, maintain adequate water intake, minimize drug meal time gaps, do not ignore pain[14], avoid taking medicine without consulting doctor.

Diagnosis: Diagnostic criteria of diabetes are as follows-

1) **Random Blood Sugar Test**- blood sugar 200mg/dl or higher indicates diabetes.
2) **Glycated haemoglobin (A1C) test** -It indicates average blood sugar level for past 2-3 past months, >6.5% Hb $_{A1C}$ indicates diabetes.
3) **Fasting Blood Sugar Level**: A blood sample is taken after an overnight fast, >126 mg/dl indicates diabetes.
4) **Oral Glucose Tolerance Test**: A blood sample is taken after an overnight fast, >200 mg/dl indicates diabetes [6].
5) **Glucose Challenge Test:** This test is also known as glucose screening test, it estimates blood glucose level in pregnant women checking them for gestational diabetes. In this test blood sample is withdrawn one hour after drinking a sweet liquid containing glucose. If blood glucose is between 135-140 mg/dl or more you are suffering from gestational diabetes.

Synthetic sources of anti-diabetic drugs: Oral hypoglycaemics are useful in the treatment of type II diabetes who does not respond adequately to non-medical interventions.
Sulfonylureas: They stimulate pancreas to make more insulin. They reduce blood glucose.
E.g. First generation: Short acting-Tolbutamide; Intermediate acting- acetohexamide, Tolazamide; Long acting- Chlorpropamide;
Second generation: Short acting-Glipizide; Long acting-glimepiride, glyburide. Side effects-Hypoglycaemia, weight gain.
Biguanides: They decrease the amount of glucose produced by the liver. E.g. Metformin. Side effects-Gastrointestinal upset including nausea, vomiting, anorexia and diarrhoea.
Thiazolidinediones: They increase the sensitivity to insulin. They exhibit glucose lowering effects and lower triglyceride levels. E.g. Pioglitazone, rosiglitazone. Side effect- hepatotoxicity.
Alpha-glucosidase inhibitors: They slow down absorption of glucose after a meal limiting postprandial hyperglycaemia.
E.g. Acarbose, miglitol, voglibose. Side effects-flatulence and other gastrointestinal symptoms.
Amylin analogues: Amylin is secreted along with insulin .E.g. Pramlintide.
Incretin mimetics: Glucagon-like-polypeptide1 (GLP) analogues: Exenatide, liraglutide.
Dipeptidyl peptidase-4 (DPP-4) inhibitors: They inhibit the enzymatic degradation of glucagon-like peptide1 (GLP-1).They limit postprandial hyperglycaemia.
E.g. Sitagliptin, saxagliptin[8]. Side effect- Hypoglycaemia.
Sodium glucose cotransporter 2(SGLT2) inhibitors: Dapagliflozin, Canagliflozin.

Insulin: Insulin is a hormone which is made by beta cells of islets of pancreas, it allows the body to use glucose. It helps to keep blood sugar level normal in hyperglycaemic or hypoglycaemic conditions. If there is more sugar present in the body insulin helps to store the excess sugar in liver and releases as per need of the body[9]. Body of patients suffering from Type -I diabetes does not secrete any insulin so, insulin is the only treatment which is effective in this type.

Various types of insulin used to treat diabetes-Rapid acting insulin: Insulin lispro(Humalog), Insulin aspart (Novolog), Insulin glulisine (Apidra).

Intermediate acting insulin: Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N), Insulin zinc (Lente). Long acting insulin: Insulin glargine(Lantus), Insulin detemir (Levemir). [22]

Disadvantages of various drug sources:
Synthetic Source: Weight gain, low blood sugar, upset stomach, gas, bloating and diarrhoea, kidney complications, risk of anaemia, tiredness or dizziness, swelling of legs or ankles[10].

Insulin- expensive, local pain, weight gain, inconvenience of multiple injections, insulin oedema, insulin allergy, resistance. Currently available medicines have adverse effects due to many disadvantages of synthetic sources it is necessary to develop safe medicine to treat diabetes and hence we focus towards herbal sources of drugs. Medicinal plants are vital in management of diabetes and complications associated with it.

Advantages of herbal medicines
Herbal medicines are generally non-toxic, they have mild action and contraindications are minimal ,reduced risk of side effects. Effective in chronic condition, lower cost as they are mostly produced from various plants or herbs , widespread availability, promote natural healing, better compatibility , herbal medicines have tendency to enhance body's natural healing process and it strengthens immunity. Safe as they are produced using natural ingredients and are chemical free. Herbal medicines treat the root cause of the problem to cure the specific system and provide permanent relief from disease.[10]

Herbal anti-hyperglycaemic agents segregated on the basis of parts of the plant used : [10,11,16,17,18,19,20,21,23,24]

Botanical Name	*Common Name*	*Family*	*Parts Used*	*Chemical Constituents*
Allium cepa	Onion	Liliaceae	Bulbs	Allicin, quercetin, dipropyl disulphide, vitamins.
Allium sativum	Garlic	Liliaceae	Bulbs	Ajoene, S-allyl cysteine, S-allylmercatocystein.
Acacia arabica	Babul	Leguminosae	Seeds, stem, bark	Octaconsanol, botulin, leucocyanidin, tannin, iso-quercetin, beta sitosterol.
Citrullus colocynthis	Badi indrayan	Cucurbitaceae	Seeds	Tannins, anthranol, flavonoids, cucurbitacin A-E, alpha tocopherol, linoleic acid, iso-vitexin.
Cajanus cajan	Tuvar	Fabaceae	Seeds	2'hydroxygenistein, cajanin, cahanones, tannins, proteins.
Trigonella foenum graecum	Fenugreek	Fabaceae	Seeds	Trigonelline, cinnamic acid, galactomannan, flavonoids, scopoletin.
Linium ustiatissimum	Flax	Linaceae	Seeds	Linoleic acid, lignans, cyanogenic glycosides, oleic acid, linolenic acid.
Vitis vinifera	Grapes	Vitaceae	Seeds	Delta-viniferins, anthocyanins, balanocarpol, resveratrol.
Cuminum cyminum	Cumin	Apiaceae	Seeds	Cuminic alcohol, safranal, p-cymene, beta sitosterol, cuminal.
Mucuna pruriens	Kiwach	Leguminosae	Seeds	Tetrahydroisoquinolines, anthraquinones, tannins, flavonoids, terpenoids.
Caesalpinia bonducella	Karanju	Caesalpiniaceae	Seeds	Bonducellin, caesalpinin, caesalpinianone, alpha caesalpin, beta caesalpin.
Citrullus lanatus	Water melon	Cucurbitaceae	Seeds	Flavonoids, alkaloids, terpenoids, balsams.
Silybum marianum	Milk thistle	Asteraceae	Seeds	Oleic acid, palmitic acid, flavonoids, stearic acid.
Solanum lycopersicum	Tomato	Solanaceae	Seeds	Campesterol, sitosterol, beta sitosterol.
Apium graveolens	Celery	Apiaceae	Seeds	Oplopandiol, bergapten, isofraxidin, D-allitol, lulularin, beta sitosterol.
Commiphora mukul	Guggul	Burseraceae	Oleogum resin	Sesquiterpenoids, diterpenoids, guggulterols, lignans,monoterpenoids, steroids.
Butea monosperma	Palara	Fabaceae	Flower	Monospermoside,butein, ,isobutrin, isocoreopsin, coreopsin, flavonoids, butin.
Cassia auriculata	Tarwar	Leguminosae	Flower	Dodecanoic acid, dimethoxyacetophenone, stigmasta, linoleic acid.
Musa sapientum	Kela	Musaceae	Flower	Flavonoids, quercetin, leucocyanidin, tannins.
Terminalia belerica	Behda	Combretaceae	Fruits	Phyllembin, chebulagic acid, ellagic acid, hexahydroxy diphenic acid ester3,4.
Capparis decidua	Karira	Capparidaceae	Fruits	Isocodonocarpine, capparisesterpenolide, capparilin, capparinin,decidua terpenolides A-E.
Eugenia jambolana	Jamun	Myrtaceae	Fruits	Jamboline, melic acid, gallic acid, oleanolic acid, anthocyanins, beta-sitosterol.
Momordica cymbalaria	Kadavanchi	Cucurbitaceae	Fruits	Cucurbitane triterpenoids, carotenoids, phytosterols, flavonoids.
Punica granatum	Anar	Lythraceae	Fruits	Punicalagin, punicalin, flavonoids, tannins.
Momordica charentia	Bitter gourd	Cucurbitaceae	Fruits	Momordicin, charantin, momordicinin, momorcharins, cucurbitin, cucurbitacin.
Vaccinium corymbosum	Blueberry	Ericaceae	Fruits	Quercetin, isoquercetin, astragalin, isomyricitrin, triliroside, 5-O-caffeoylqunic acid.
Terminalia chebula	Hirda	Combretaceae	Fruits	Chebulic acid,chebulin,chebulosides I and II, punicalagin,terflavin A and B,terchebin.
Terminalia catappa	Deshibadam	Combretaceaea	Fruits	Alpha-farnesene,neoisothujol,bexadecanoic acid, dibutyl phthalate.

Botanical Name	*Common Name*	*Family*	*Parts Used*	*Chemical Constituents*
Gymnema sylvestre	Gurmar	Asclepidaceae	Leaves	Gymnemic acid, gymnemasaponins, gymnemasides, anthraquinones.
Hibiscus rosa-sinesis	Gudhal	Malvaceae	Leaves	Anthocyanins, flavonoids, quercetin-3,7-diglucoside, hentriacontane.
Lanata camara	Wild-sage	Verbenaceae	Leaves	Sesquiterpenes, curcumene, safrole, lantadene A,B,C,D, falvonoids.
Lagerstroemia speciosa	Banaba	Lythraceae	Leaves	Corosolic acid, maslinic acid, lagerstroemia, reginin A, ellagic acid, beta-sitosterol.
Mangifera indica	Aam	Anacardiaceae	Leaves	Mangiferin, hyperin, quercetin3-O-beta glucopyranoside.
Morus alba	Shetut	Moraceae	Leaves	Anthocyanins, flavonoids, glycopeptides.
Memecylon umbellatum	Anjani	Melastomataceae	Leaves	Phytosterols, terpenoids, glycosides, tannins, flavonoids, amino acids.
Ocimum sanctum	Tulsi	Labiatae	Leaves	Cirsilineol, circimaritin, isothymusin, apigenin, rosameric acid, eugenol, carvacrol.
Swertia chirayita	Chirata	Gentianaceae	Leaves	Chirantin, ophelic acid, amarogentin, sweroside swertiamarin, mangiferin, swerchirin,.
Semecarpus anacardium	Bhallatak	Anacardeaceae	Leaves	Bhilwanols, bioflavonoids, nallaflavonone, anacarduflavone,semecarpetin,jeediflavanone.
Plantago ovata	Isabgol	Rutaceae	Leaves	Epiloganic acid, gardoside, plantamajoside, arabinose, iridoids.
Acacia nilotica	Babool	Fabaceae	Leaves	Kaempferol,tannins, quercetin, phytosterols, ellagic acid, saponins.
Eugenia uniflora	Pitanga	Myrtaceae	Leaves	Flavonoids, triterpenoids, anthraquinones, phenols.

Ipomoea batatas	Sweet potato	Convolvulaceae	Leaves	Abietadiene, beta caryophyllene, spathulenol, cis-sabinene,alpha-bergamotol.
Murraya koehigii	Curry leaf	Rutaceae	Leaves	Girinimbine, bismahanine, mahanimbine, koenine, koenidine, girinimbiol.
Cinnamomum tamala	Tejpat	Lauraceae	Leaves	Myrcene, alpha-pinene, camphene, eugenol, limonene,p-cymene.
Olea europaea	Olive	Oleaceae	Leaves	2-methoxy-3-isopropylpyrazine, alpha-pinene, maslinic acid, nonsterol triterpenoids.
Centella asiatica	Gotu kola	Apiaceae	Leaves	Asiaticoside, Asiatic acid, madecassic acid, alpha-pinene, brahmic acid.
Rosmarinus officinalis	Rosemary	Lamiaceae	Leaves	Rosmarinic acid, cymene, 8-cineol, camphene, beta-myrecene.
Carica papaya	Caricaceae	Papaya	Leaves	Carpain, pseudocarpin, dehydrocarpaineI and II, carposide, choline.
Ananas comosus	Bromeliaceae	Pineapple	Leaves	Triterpenes, ergosterol, stigmastene-diol, campestanol, campesterol.
Phyllanthus niruri	Keezhanelli	Euphorbiaceae	Leaves	Hypophyllanthine, cymene, astragalin, niranthin, niruretin, niruriside.
Aloe barbadensis	Aloe	Asphodelaceae	Leaves	Aloe emodin, barbaloin, aloetic acid, vitamin A, B, C, E.
Artemisia pallens	Davana	Compositae	Leaves	Davanone, davana furan, farnesol, sesquiterpene lactones, germacranolides, methyl cinnamate.
Aegle marmelos	Bael	Rutaceae	Leaves	Furocoumarins,xanthotoxol, marmesin, rutin, o-methylhafordinol, flavonoids.
Andrographis paniculata	Kalmegh	Acanthaceae	Leaves	Andrographolide,andrographin, neoandrographolide,deoxyandrographolide, andrographoside.
Adhatoda vasica	Adulsa	Acanthaceaea	Leaves	Vasicine, vasicine acetate, vasicinone, anisotine, isovitexin, adhatodine, daucosterol.
Anacardium occidentale	Kaju	Anacardiaceae	Leaves	Methyl chavicol, germacrene B, beta copaene, linalool, alpha-cadinol ,beta bisabolene.
Annona squamosa	Seetaphal	Annonaceae	Leaves	Aetogenin,sesquiterpenes, alpha-cadinol, alkaloids.
Azadirachta indica	Neem	Meliaceae	Leaves	Nimbin, quercetin, nimbosterol, nimbidin.
Bauhinia forficata	Brazilian orchid tree	Leguminosae	Leaves	Astragalin,kaempferitrin,quercitrosides, rhamnose, flavonoids, glycosides.

Botanical Name	*Common Name*	*Family*	*Parts Used*	*Chemical Constituents*
Teucrium cubense	Coastal germander	Lamiaceae	Leaves	Carvacrol, sabinene, beta caryophyllene, alpha-pinene, beta-pinene.
Terminalia superb	Afara terminalia	Combretaceae	Leaves	Flavonoids, polyterpens, polyphenols.
Tecoma stans	Yellow trumpetbush	Bignoniaceae	Leaves	Ursolic acid, chlorogenic acid, caffeic acid, oleanolic acid.
Ocimum album	Holy basil	Lamiaceae	Leaves	Sabinene,copaene, italicene, tetradecanal, phytone, alpha pinene.
Sesbania sesban	Common sesban	Fabaceae	Leaves	Lignoceric acid, palmitic acid, kaempferol, lupeol, galactomannan.
Prunus persica	Peach	Rosaceae	Leaves	Hentriaontane,beta sitosterol, ursolic acid,
Origanum vulgare	Oregano	Lamiaceae	Leaves	Kaempferol,daucosterol, pillion, genistein, luteolin, hyperin.
Catharanthus roseus	Sadabahar	Apocynaceae	Leaves	Dotriacontane, limonene, dodecyl alcohol, geraniol, hexadecanoic acid, citral, stearic acid.
Coccinia indica	Kanturi	Cucurbitaceae	Leaves	Heptacosane, cephalandrol ,beta sitosterol.
Combretum micranthum	Kinkeliba	Combretaceae	Leaves	Vitexin, orientin, homoorientin, myricetin, stachydrine, kinkeloids A-D.
Boerhavia diffusa	Punarnava	Nyctaginaceae	Leaves	Beta sitosterol, tetracosanoic acid, hexacosonoic acid, urosolic acid, hentricontane, triacontanol.
Biophytum sensitivum	Lajjalu	Oxalidaceae	Leaves	Cuppressuflavone, amentoflavone, iso orientin, 4-caffeoylquinic acid, luteolin-7-metyl ester.
Bacopa monniera	Brahmi	Scrophulariaceae	Aerial parts	Bacopasides I-XII, brahmine, herpestine, apigenin, monnierasidesI-III, bacosides.

Marketed formulations: [17,25]

S. No	Formulation	Formulation Type	Herbs Used
1.	Diabecure	Tablet	Berberis vulgaris, Erytherea centaurium, Juglans regia, millefolium taraxacum.
2.	Diasulin	Capsule	Cassia auriculate, Coccinia indica, Momordica charantia, syzygium cumini, Emblica officinalis, Trigonella foenum graecum, Curcuma longa, Gymnema sylvestre, Tinospora cordifolia, Scoparia dulcis.
3.	BGR 34	Tablet	Berberis aristata, Pterocarpus marsupium, Gymnema sylvestre, Rubia cordifolia, Tigonella foenum graecum, Tinospora cordifolia.
4.	Diarid	Capsule	Pterocarpus marsupium, Berberis aristate, Cocinum fenestratum, Emblica officinalis, Symplocos racemosa, Vetiveria zizanioides, Curcuma longa, Salacia reticulata.
5.	Madhumehantak churna	Powder	Azadirachta indica, Berberus aristate, Pterocarpus marsupium, Gymnema sylvestre, Trigonella foenum graecum, Momordica charantia, Aegle marmelos, Syzygium cumini, Salacia chinensis, Acacia arabica, Eochnera rosea, Ocimum sanctum.

2. Conclusion

Diabetes is a chronic disorder associated with many complications in order to prevent these problems there is need to develop new anti-diabetic formulations .This paper shows the plants with anti-hyperglycaemic agents that are used in treatment of diabetes and may be helpful for scientists, health professionals and scholars developing anti-

diabetic formulations. Herbal drugs need further exploration for development of drugs and nutraceuticals. These plants increase the insulin output or decrease in absorption of glucose.

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Author Profile

Darakhshan Shaikh has completed her Master of pharmacy degree in Quality Assurance department in 2015. She is working as an Assistant professor in Oriental College of Pharmacy in QA department and pursuing PhD as well.

Rashmi Patil has completed B-Pharmacy from Mumbai University in 2017. Currently she is pursuing Master of Pharmacy in Quality assurance department at Oriental college of pharmacy.