A Comprehensive Review On Role Of Phytochemicals In The Management Of Diabetes Mellitus.

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Abstract: Diabetes mellitus is characterized by alterations in the metabolism of carbohydrate, fat and protein caused due to insulin secretion deficiency and different levels of insulin resistance. Global increase in the incidence of diabetes becoming a great threat to the human beings .Hyperglycemia is one of the prevailing condition of Diabetes mellitus which gives rise to various diabetic complications like diabetic nephropathy, retinopathy, neuropathy, delayed wound healing, heart attack, peripheral vascular disturbances and ketoacidosis. Medicinal plants contain micronutrients, amino acids , protein, mucilage, essential oils, triterpenoids, saponins, carotenoids, alkaloids, flavonoids, phenolic acids, tannins and coumarins, which play an effective role in the prevention and treatment of Diabetes mellitus. This review article indicates that the potent phytoconstituents with their mechanism of action which have involved in the management of Diabetes mellitus.

Key words: Diabetes mellitus, Complications, Phytoconstituents

Introduction

Diabetes mellitus is the world's largest endocrine disorder characterized by developing insulin resistance, impaired insulin signaling, B cell dysfunction, abnormal glucose, protein and and lipid metabolism. WHO recognizes three main forms of diabetes mellitus: type 1, 2 and gestational diabetes. According to IDF (International Federation Of Diabetes),type 2 diabetes mellitus accounts for about 90% of all diabetes incidences..[1] In diabetic patients, late complications like Retinopathy, nephropathy, autonomic neuropathy, cardiovascular atherosclerosis and obesity etc. develops. Global increase of diabetes mellitus was estimated to be 2.8 % in 2000 to 4.4 % in 2030. Worldwide, the total number of people with diabetes mellitus is projected to rise from 171 million in 2000 to 366 million in 2030. International Diabetic Federation (IDF) estimate about 8.3 % of adults, over all 382 million people all over the world and about 65.1 million people in India with diabetes mellitus. It will reach beyond 592 million in further 25 years.[2]

Diabetes mellitus 1 and Diabetes mellitus 2 can be differentiated on the basis of some specific features listed in table No.1

Table 1: Comparision of type 1 and type 2 diabetes mellitus. [3]

Feature	Type-1 Diabetes	Type-II Diabetes
Age at onset	Early (below 35 years)	Late (after 40 years)
Type of onset	Abrupt and severe	Gradual and insidion
Frequency	10-20%	80-90%
Weight	Normal	Obese/non-obese
Genetic locus	Unknown	Chromosome 6
Pathogenesis	Autoimmune destruction of β-Cells	Insulin resistance, impaired insulin secretion
Blood insulin level	Decreased insulin	Normal or increased insulin
Islet cell changes	Insulitis, β-cell depletion	No insulitis, later fibrosis of islets
Clinical management	Insulin and diet	Diet, exercise, oral drugs, insulin

Current Therapy for Diabetes mellitus: There are various therapies used for the treatment of Diabetes mellitus such as allopathic, ayurvedic, naturopathy, yoga, siddha and homeopathic.

Allopathic Therapy:

Different synthetic drugs are available for diabetes mellitus management. Synthetic insulin formulation is given in Diabetes mellitus patients to control blood glucose level,which results in weight gain, allergy, resistance and may lead to hypoglycaemia. Many drugs are available in the form of Oral hypoglycaemics like Sulfonylureas, Biguanides- metformin, α-glucosidase inhibitors, Thiazolidienediones, Glucagon like peptide-1 agonist, Amylin analog, Peroxisome proliferator, Dipeptidyl peptidase-4 inhibitors, Bile acid sequestrant and Dopamine agonist, which are being used globally for the treatment of diabetic mellitus patients. The long-term use of these synthetic drugs and insulin in Diabetes mellitus patients result in various side effects such as hypoglycemic episodes, gastrointestinal problems like nausea, vomiting, diarrohea, edema and hepatorenal disturbance .[4]

Yoga therapy:

Yoga improves the general feeling of well being. This therapy provides an ideal cure for diabetes management. Yogic practices like Sirsasana, Veerasana, Katichakrasana, Mayurasana, bhujangasana, Nauli, Bhastrika pranayama help in restoring the pancreas action and to regulate the deficiency of insulin secretion.[5]

Homeopathic therapy:

Homeopathy has a vital role to play in the cure and management of diabetic patients. Phosphorus, aurum metallicum,uranium nitricum, arsenicum bromatum, phosphoric and lactic acid are used effectively in the treatment of diabetes mellitus. [6]

Unani therapy:

The unani therapy believes that cure of Diabetes is possible through energizing the pancreatic cells. carrot, eucalyptus, fennel, geranium and lemon oils have a restoring and rejuvenating effect on the pancreas. [7]

Naturopathy:

Nature cure has the power to control diabetes at the earliest. Mud therapy, hydrotherapy, massage therapy, sun bath and exercise are found beneficial in treatment of diabetic patients. [8]

Role of natural products in the treatment of Diabetes mellitus

The use of medicinal plants to treat human diseases has its roots since timeimmeorial. Antihyperglycaemic effects of these plants are attributed to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes.vWHO has recommended Traditional medicines as the primary source of health care because of their easy accessibility, affordability, cultural acceptability and trust by people. In traditional medicine system, several medicinal plants have been used globally to prevent long-term complications in the management of diabetes. About 200 pure bioactive compounds from different chemical groups like phenolic acids, flavonoids, triterpenoids, alkaloids, glycosides and carbohydrates have been isolated from medicinal plants which shows strong antidiabetic properties exhibited by regulation of blood glucose level and the metabolic disturbances through a variety of mechanisms. [8]

About Four billion individuals of the world's population in developing countries rely on traditional medicine as the primary source of health care.[9] The use of medicinal plants and phytoconstituents may delay the development of diabetic complications .It is important to note that each medicinal plant contains thousands of phytochemicals of which only few are therapeutically effective. In addition, the yield of phytochemicals depends on different plant parts i.e. barks, leaves, flowers, roots, fruits or seeds and their extraction methods .[10]

Phytochemicals used in the management of diabetes mellitus

Alkaloids

Alkaloids are secondary plant metabolites containing basic nitrogen atoms and are also found in bacteria, fungi and other animals. Alkaloids are classified as (1) True alkaloids like nicotine, atropine, morphine; (2) Protoalkaloids like mescaline, adrenaline, ephedrine;(3) Polyamine alkaloids like

putrescine, spermidine and spermine; (4) Pseudoalkaloids like caffeine, theobromine, theophylline etc; (5) Peptide and Cyclopeptide alkaloids.

The alkaloid berberine, extracted from the plant *Tinospora cordifolia*, enhances the hexokinase and phospho fructo kinase activity resulting in glucose transport, carbohydrate digestion and absorption[1]. Vinblastine and vincristine are isolated from *catharanthus roseus*, which activate free radical scavenging enzymes.[11]

Growing evidences proves the ability of specific alkaloids to intervene in the insulin-signal transduction pathway, reverse molecular defects resulting in insulin resistance and glucose intolerance and improve complications of Diabetes mellitus.

Tannins

Tannins are polyphenolic biomolecule found naturally in berries, nuts, legumes, chocolate, spices and herbs.[12] Tannins are classified into 2 major classes ,(1) Hydrolyzable tannins like gallic acid ,(2) Non-hydrolysable or condensed tannins like flavones and Phlobotannins Condensed tannins obtained from α-amaranth grain, finger millet, field bean, sunflower seed, drumstick and amaranth leaves shows anti-diabetic potential mainly by inhibiting the activation of α-amylase and α-glucosidase activities.[13]

Flavonoids

Flavonoids are group of soluble polyphenolic compounds found abundantly in fruits, vegetables, nuts, seeds, stem, flowers, and green tea. Chemically, they have the general structure of a 15-carbon skeleton consisting of two phenyl rings and heterocyclic ring.[14] Natural flavonoids are classified into six classes (1) anthocyanidins (2) flavan-3-ols (3) (4) flavones (5) flavanones (6) isoflavones .The anti-diabetic properties of flavonoids are attributed partly to their antioxidant potentials and partly due to their ability to modulate some cell signalling. Flavonoids alternate the diabetes treatment by reducing the aldose reudctase, regenerating the pancreatic cells, enhancing insulin release and by incresing calcium ion uptake.[15] Quercetin, Apigenin, Rutin, Apigenin-7-O-glucoside and Naringenin are important phytoconstituents found in *Panax notoginseng Urtica dioica*, *Bauhinia varigtla* and *Camellia sinensis* actively involved in the pancreatic β-cell restoration and insulin secretion. Aegelin, Marmesin, Marmelosin, Momordin, momordicine, Charantin, Momorcharaside A and B, Momorcharin A and B, Cucurbitacin B decrease insulin resistance. Deprived solubility and bioavailability are responsible for their limited use.[16]

Saponins

Saponins are surface active plant glycosides which act as a chemical barrier in the plant defense system against pathogens and herbivores. They have scientific attention due to their structural diversity and significant biological activities. They are composed of sugar moieties linked to a hydrophobic aglycone part, known as sapogenin. Saponins consists of anti-inflammatory, antifungal, antibacterial, antiparasitic, antitumor, antiviral and antidiabetic properties .Saponins regulates gluconeogenesis and glucose uptake in diabetic patients by activating AMPK in a calcium-dependent manner.[16] Lactucain C obtained from *Lactuca indica* was found to produce significant antihyperglycaemic activity.[17]

Polysaccharides

Polysaccharide shows antidiabetic effect by increasing serum insulin level, reducing the blood glucose level and by improving glucose tolerance. Natural polysaccharides have been found beneficial for the treatment of hypoglycaemia .Carbohydrate digestion and absorption are regulated by L-arabino-D-xylan, Cinnzeylanin, Cinnzeylanol and D-glucan, which are extracted from *Cinnamomum zeylanicum*[18], etc. There are number of plants and their active constituent are present in the table 2 which is beneficial for diabetes disease.

Table : 2

Chief constituent	Biological source	Role in the treatment	Refe rnce
Diosmin Flavonod	*Scrophularia nodosa*	It decreases the level of glycosylated haemoglobin, increases the activities of glutathione peroxidases, significant reductions in plasma glucose values, increases hepatic hexokinases and glucose-6-phosphate dehydrogenases	19
Fisetin Flavonod	*Cotinus coggygria*	Inhibit gluconeogenesis through inhibition of mitochondrial pyruvate transport and decreases the cytosolic NADH/NAD redox.	20
Morin Flavonod	*Chlorophora tinctoria Psidium guajava*	Reduce glucose-6-phosphatase activities, increase hexokinase, glucose-6-phosphate dehydrogenase activities and improve insulin levels.	19
Hesperidin Flavonoid	*Citrus aurantium*	Down regulating the generation of free radicals& release of proinflammatory cytokines.	19
Naringenin Flavonoid	*Citrus fruits and tomatoes*	Inhibits α-glucosidase activities. Activation of 5′AMPactivated protein kinase (AMPK), enhancement ofantioxidant activities and reduction of insulin resistance.	21
Baicalein Flavonoid	*Oroxylum indicum*	Up-regulation of AMPK, induces insulin Production and suppresses the activation of NF-kB.	19
Chrysin Flavonoid	*Tilia tomentosa*	Suppression of TGF-β, fibronectin, and collagen-IV protein expression. It improves insulin levels.	19
Luteolin Flavonoid	*cabbage*	Potentiate insulin action and increase transcriptional activation of PPARγ.	19
Wogonin Flavonoid	*Scutellaria baicalensis*	Interferes with insulin sensitivity and lipid metabolism through its effect on AMPK and PPARα6.	22
Isorhamnetin Flavonoid	*Hippophae rhamnoides*	Reduces oxidative stress, inhibits sorbitol accumulation and interferes with lipid metabolism.	23

Kaempferol Flavonoid	*Ginkgo biloba*	Reduction of caspase-3 activity in beta cells, improvement of cAMP signalling and enhancement of insulin production and secretion.	19
Daidzein Flavonoid	*Glycine max*	Improves lipid and glucose metabolism, insulin sensitivity and enhances AMPK phosphorylation in muscles.	19
Bengalenoside Flavonoid	*Ficus benghalensis*	α-glucosidase inhibitory activity.	24
Epigallocatechin gallate	*Camellia sinensis*	Increases insulin activity.	25
Genistein Flavonoid	*Glycine max*	Act as a hypoglycemic peroxisome proliferator and activated receptor (PPAR) agonist.	26
Jamboline Glycoside	*Syzygium cumini*	prevent conversion of starch into sugar	27
Myrciacitrins I and II flavanone glucosides	*Myrcia multiflora*	Inhibitory action on aldose reductase and alpha-glucosidase.	28
Neomyrtillin Glycoside	*Vaccinium myrtillus*	Enhance the hypoglycemic action of exogenous insulin.	19
Leucopelargonidn Glycoside	*Ficus bengalensis*	stimulate insulin secretion.	19
Pseudoprotinosaponin AIII Glycoside	*Anemarrhena asphodeloides*	Actions on hepatic gluconeogenesis or on glycogenolysis.	29
Vitexin Glycoside	*Microcos paniculata*	□-glucosidase inhibitory effects.	19
Securigenin Glycoside	*Securigera securidaca*	Increase in insulin secretion.	30
Andrographolide Alkaloid	*Andrographis paniculata*	α-glucosidase inhibitory activity.	19
Trigonelline Alkaloid	*Trigonella foenum-graecum*	Acts by affecting cell regeneration, insulin secretion.	31
Magnoflorine Alkaloid	*Tinospora cordifolia*	Stimulate insulin secretion from the RINm5F cell line	1
Javaberine Alkaloid	*Talinum paniculatum*	Inhibitors of TNF-□ production by macrophages and fat cells.	1
Lepidine Alkaloid	*Lepidium sativum*	By potentiating pancreatic secretion of insulin from the remaining islet β cells.	32

Lupanine Alkaloid	*Lupinus perennis*	Enhanced glucose-induced insulin release from isolated rat islet cells	33
Mahanimbine Alkaloid	*Murraya koenigii*	alpha-glucosidase inhibitor.	1
Piperumbellactam Alkaloid	*Piper umbellatum*	Inhibition of α-glucosidase enzyme.	1
Radicamines Alkaloid	*Lobelia chinensis*	alpha-glucosidase inhibitor.	1
Schulzeines Alkaloid	*Penares schulzei*	Inhibits α-glucosidase.	34
1deoxynojirimycin Alkaloid	*Morus alba*	α-glycosidase inhibitors.	1
Bassic acid Trepenoid	*Bumelia sartorum*	Acts by increasing glucose uptake and glycogen synthesis.	35
Charantin Terpenoid	*Momordica charantia*	Stimulates the release of insulin.	36
Christinin-A Saponin glycoside	*Zizyphus spina-christi*	Improvement in glucose utilization.	1
Colosolic acid Terpenoid	*Lagerstroemia speciosa*	Act as glucose transport activator.	37
Elatosides E Terpenoid	*Aralia elata*	Affect the elevation of plasma glucose levels.	38
Forskolin Terpenoid	*Coleus forskohlii*	Stimulates glucose-induced insulin secretion.	39
Gymnemic acid	*Gymnema sylvestre*	Inhibits the glucose absorption , increases glucose uptake in striated muscles.	40
Momordin Saponin	*Kochia scoparia*	Inhibit glucose and ethanol absorption.	41
B-sitosterol Glycoside	*Azadirachta indica*	Inhibits glucose-6-phosphatase enzyme.	42
Senegin Triterpene glycoside	*Polygala senega*	Reduce blood glucose levels.	1
Glucomannan Polysaccharide	*Amorphophallus konjac*	Delay the rate of glucose absorption.	1
Bellidifolin Glycoside	*Swertia japonica*	Stimulate glucose uptake activity.	43
Curcumin Alkaloid	*Curcuma longa*	α-glucosidase inhibitory action.	1
Chebulanin	*Terminalia*	Intestinal maltase inhibitory	44

	chebula	activity.	
Ferulic acid	*Curcuma longa*	Stimulates insulin secretion	1

Conclusion

Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to the diminished insulin production or insulin resistance. Bioactive anti-diabetic principles of plant origin are mainly phytochemicals which include but not limited to flavonoids, saponins, alkaloids, tannins, terpenes, and glycosides. A lot of studies have been carried out in several medicinal plants in regard to management of Diabetes mellitus. Results indicated that many medicinal plants possess anti-diabetic potentials and also demonstrated specific bioactive anti-diabetic principles and various mechanisms of actions of these agents. The data on phytochemicals compiled in this review provide a lead with respect to diabetes management, showing the regulatory effects on various steps of different metabolic pathways that may have therapeutic applications in the treatment of Diabetes mellitus. Although recent progress has been made in understanding the underlying mechanisms and diverse activities of these plant derived constituents, further studies are required to firmly establish their mechanisms of actions.

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