



Type 2 Diabetes, Therapeutic Targets and Potential Drugs: A Review

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Abstract: Type 2 diabetes mellitus (T2DM) is very common diseases and results from a combination of defects in insulin secretion and insulin action, either of which may predominate. This type of diabetes accounts for 90 to 95% of all diabetic patients. The current prevalence of T2DM is 2.4% in the rural population and 11.6% in the urban population of India. The present review gives a brief introduction to various therapeutic targets for Non Insulin Dependent Diabetes Mellitus (NIDDM) and available drugs which can activate/inhibit the receptors and expected to lower low density lipoprotein (LDL) cholesterol and triglycerides, raise high density lipoprotein (HDL) cholesterol, and normalize hyperglycaemia. The increasing incidences of T2DM, represents a considerable public health problem and is characterized by loss in sensitivity of tissues towards insulin which can be restored by activation of peroxisome proliferator-activated receptors (PPARs), members of nuclear receptor family which are functioning as ligand dependent transcription factor. The present paper also reviews medicinal plants that have shown experimental or clinical antidiabetic activity and that have been used in traditional systems of medicine.

Keywords: Type 2 diabetes mellitus; peroxisome proliferator-activated receptors; non insulin dependent diabetes mellitus; low density lipoprotein; high density lipoproteins.

I. Introduction

Diabetes mellitus (DM), long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century [1]. It is the most common non-communicable disease worldwide and the fourth to fifth leading cause of death in developed countries [2]. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025 [3]. Developing countries such as India has seen the maximum increase in the last few years. The current prevalence of type 2 diabetes is 2.4% in the rural population and 11.6% in the urban population of India. It has been estimated that by the year 2025, India will have the largest number of diabetic subjects in the world [3]. DM is a heterogeneous group of disorders characterized by high blood glucose levels [4].

II. Cause of T2DM

Type 2 Diabetes Mellitus (T2DM) is a non-autoimmune, complex, heterogeneous and polygenic metabolic disease condition in which the body fails to produce enough insulin, characterized by abnormal glucose homeostasis [5]. Its pathogenesis appears to involve complex interactions between genetic and environmental factors [5]. T2DM occurs when impaired insulin effectiveness (insulin resistance) is accompanied by the failure to produce sufficient cell insulin [6].

T2DM as a common and complex disease has been characterized by the following causes:

Obesity: obesity is also considered a key risk factor for T2DM. The association between increasing body mass index (BMI) and greater weight gain and risk of diabetes is most pronounced among Asians, suggesting that lower cut off BMI values are needed to identify Asians at a higher risk of diabetes [7] BMI cut point for Indians for any cardio metabolic risk factors is 23 kg/m² in both sexes, whereas that of waist circumference (WC) is 87cm for men and 82cm for women [8].

Abdominal adiposity: there is also a probable indication that there is a preferential abdominal adiposity in Indians irrespective of the degree of general adiposity [9].

Imbalance of human metabolism is associated with T2DM: Changes in work patterns from heavy labor to sedentary, the increase in computerization and mechanization, and improved transport are just a few of the changes that have had an impact on human metabolism [10].

Ethnicity: the interethnic differences (like differences in prevalence of T2DM among Europeans, Americans, Chinese, and Asian Indians) in insulin resistance may have an environmental or genetic explanation. The main acquired factors that seemingly increase insulin resistance in all ethnic groups include obesity, sedentary lifestyle, diet rich in animal products, and aging [11].

III. Complications of Diabetes in India

The burden of diabetes is to a large extent the consequence of macrovascular (coronary artery disease, peripheral vascular disease, and atherosclerosis) and microvascular (like retinopathy, neuropathy, and nephropathy) complications of the disease [6]. The increasing incidences of type 2 diabetes and their consequences in terms of cardiovascular morbidity and mortality represent a considerable public health problem [12]. Therefore, identification of the molecular targets of the transducers critically involved in the control of glucose and lipid homeostasis is crucial for developing new therapeutic agents for the treatment of metabolic syndrome.

IV. Receptors

Metabolic nuclear receptors (NR) are particularly attractive target molecules, since they have been found to play a central role in maintaining cellular and whole-body glucose and lipid homeostasis. Among these receptors, special attention has been paid for more than a decade to the members of the peroxisome proliferator-activated receptor (PPAR) family [13].

V. PPARs

PPARs belong to the nuclear hormone receptor family, which is defined as transcriptional factors that are activated by the binding of ligands to their ligand-binding domains (LBDs) [14]. There are 3 PPAR subtypes namely (PPAR α [NR1C1], PPAR β [NR1C2], and PPAR γ [NR1C3] [15], which display different tissue distribution pattern and distinct pharmacological profiles [16] but they share similar three dimensional structure within LBDs. Thus ligands that simultaneously activate two or all of the PPARs could be potent candidates in terms of drugs for the treatment of abnormal metabolic homeostasis. PPAR α is mostly expressed in the tissues involved in lipid oxidation, such as liver, kidney, skeletal, cardiac muscle, and adrenal glands [17]. PPAR γ is expressed in adipose tissue, macrophages, and vascular smooth muscles [18]. PPAR γ was first identified as a master regulator of adipocyte differentiation, but more recent molecular-biological studies have indicated that PPAR γ activation is also linked to the expression of many important genes that affect energy metabolism, such as the TNF- α , leptin, and adiponectin genes [19]. Costs of synthetic drugs have escalated these days in leaps and bounds. In this situation, development of cost-effective treatment and indigenously engineered remedies become extremely essential. Chemometric modelling, which is a part of an enormous field of cheminformatics technology, has now become very popular among the researchers and the pharmaceutical industries to identify the drug targets via computational tools. Structural activity relationship (SAR) which is a statistical technique capable of analyzing screening datasets and deriving predictive models of biologically interested activity, molecular dynamics and molecular docking are already proved vital chemometric techniques to optimize the drug candidates [20]. The chemometric techniques can be used to identify important features necessary for a compound to behave as activator of PPAR- α and PPAR- γ receptors while such studies with PPAR- β/δ reveals that lead compound shows very weak PPAR- β/δ transactivation activity [21].

VI. α -GLUCOSIDASE

α -Glucosidase (EC 3.2.1.20) is an enzyme responsible for catalytic cleavage of a glycosidic bond [22]. α -Glucosidase (EC 3.2.1.20) enzyme can be an important strategy in the management of postprandial blood glucose level in type-2 diabetic patients and borderline patients as it is involved in digestion of carbohydrates significantly decrease the postprandial increase of blood glucose after a mixed carbohydrate diet [23]. In small intestine the intestinal α -glucosidase hydrolyzes complex carbohydrates to glucose and monosaccharide. The reduction in rate of digestion of carbohydrates can be achieved by inhibiting these enzyme systems [24]. In diabetics the short term effect of enzyme inhibitor drug therapies decreases high blood glucose levels [25]. α -Glucosidase has drawn a special interest of the pharmaceutical research community because it shows the inhibition of its catalytic activity in earlier studies and resulted in the decrease in postprandial blood glucose level and retardation of glucose absorption [26]. α -Glucosidase inhibitors do not cause hypoglycemic events or other life-threatening events, even at overdoses, and cause no weight gain [27]. Glucosidase inhibitors are highly useful for medical therapies, such as diabetes, obesity, hyperlipoproteinemia, cancer and HIV and hence are the potential bio-tools [28]. It has also been observed that α -Glucosidase inhibitors block viral infections and proliferation in HIV-infections [29], [30].

VI. AMPK- α

Adenosine monophosphate -activated protein kinase (AMPK) is a key sensor and regulator of intracellular and whole-body energy metabolism. AMPK is composed by a catalytic α subunit and two regulatory subunits, β and γ . These subunits are expressed in various tissues and sub cellular locations and include multiple isoforms ($\alpha 1$, $\alpha 2$; $\beta 1$, $\beta 2$; $\gamma 1$, $\gamma 2$, $\gamma 3$) [31], [32]. Cellular energy regulation and maintenance of the energy balance in the whole body is the major function of AMPK. AMPK stimulates ATP generation, glucose uptake and fatty acid oxidation upon activation, while it simultaneously inhibits the syntheses of hepatic triacylglycerol, cholesterol, protein and glycogen and down-regulates the ATP-consuming anabolic pathways [33]-[37]. AMPK- α plays a

central role in the regulation of body weight, systemic glucose homeostasis, lipid metabolism, and mitochondrial biogenesis [38], [39], due to which the activation of AMPK would be a promising therapeutics against type 2 diabetes as well as other metabolic syndromes [40]. Two first-class antidiabetic drugs, biguanides and thiazolidinediones, were proved to be related to the AMPK activation [41], [42].

VIII. Drugs for Treatment of Type II Diabetes Mellitus

Oral hypoglycemic drugs: Sulfonylureas which include tolbutamide, chlorpropamide, glibenclamide, glipizide, acetohexamide, gliclazide and tolazamide [43]; Biguanides which includes **metformin** and Phenformin [44]; and other miscellaneous drugs such as Acarbose and guar gum are most common oral hypoglycemic drugs.

Other drugs for NIDDM and their corresponding targets: The other treatment for NIDDM include insulin sensitizers, drugs which reduce resistance of tissues towards insulin by interaction with the PPAR, a nuclear receptor regulating genes involved in metabolism of lipid. The cause of insulin sensitivity is the result of decreased production of non-esterified fatty acids. The non-esterified fatty acids have the capacity to potentiate the effect of endogenous insulin. Troglitazone, which belongs to the thiazolidinedione group, is used in the treatment of T2DM. A benzoic acid derivative Repaglinide, has also been used in T2DM patients as it stimulates insulin production at meal times [45].

Thiazolidinediones: The thiazolidinediones also known as glitazones were introduced in the late 1990s [46]. Glitazones are a class of medications that activates PPARs and are used in the treatment of T2DM.

Alpha glucosidase inhibitors: The introduction of drugs which can inhibit the enzymes responsible for breakdown of carbohydrates in intestine is an alternative approach for the treatment of overweight patients with NIDDM. Acarbose is a sugar that competitively inhibits α -glucosidase enzymes, as a result of which, dietary carbohydrates are poorly absorbed, and the postprandial rise in blood glucose is reduced. Undigested starch is broken down by fermentation when it enters the large intestine. Dosage needs careful adjustment to avoid the side effects such as abdominal discomfort, flatulence and diarrhea. Since it is mainly inactivated in the gut, very little acarbose enters the circulation, but liver dysfunction may rarely occur with high doses [47].

IX. Use of Medicinal Plants for Hypoglycemic Agents

Oral hypoglycemics, dietary modification, and insulin, are the currently available therapeutic options for NIDDM, which have limitations of their own [48]. Many herbal medicines and natural products have been recommended for the treatment of NIDDM. The present paper reviews medicinal plants that have shown experimental or clinical antidiabetic activity and that have been used in traditional systems of medicine.

Table I Shows the medicinal plants used as hypoglycemic agents.

Name	Family	Part Used	Chemical Constituent	Medicinal Use	Pharmacological Activity	Study
Tussilago farfara	Asteraceae	Flower bud.	Mucilage, phytosterol, dihydride alcohol, tannin, and faradial.	Flower bud of Tussilago farfara is useful in T2DM	Anti-inflammatory, anti-spasmodic and hypoglycaemic.	α -Glucosidase inhibitory effect by the flower buds of Tussilago farfara [49].
Prinsepia utilis Royle	Rosaceae	Aerial parts.	Triterpenoids, pentacyclic.	Oil from seeds is rubifacient and is applied locally in rheumatism.	Anti-inflammatory, anti-arthritis and hypoglycaemic.	Hypoglycemic effect of flavonoids from Prinsepia utilis on alloxan-induced diabetic mice [50].
Ricinus communis	Euphorbiaceae	Root, leave, oil.	Ricinolein, ricin, flavonoids, ricinolic acid, sodium ricinoleate, tristearin.	Constipation, pain and inflammation.	Anti-inflammatory, hypoglycaemic and laxative.	Antidiabetic activity of 50% ethanolic extract of Ricinus communis and its purified fractions [51].
Aloe vera	Xanthorrhoeaceae	Leaf Gel.	Antraquinone glycosides, free anthaquinones, enzymes, antibiotic principles, resins, glucomannan, steroids, organic acids, amino acids, salicylic acid and cinnamic acid, essential oil.	Bacterial infections and Inflammation, wounds.	Anti-inflammatory, emmengogue, emollient, and antibacterial.	Hypoglycemic effect of Aloe vera gel on streptozotocin-induced diabetes in experimental rats [52].
Crataeva	Capparidaceae	Leaves.	Tannin and saponin.	Diabetes mellitus.	Hypoglycemic.	Antidiabetic

nurvala Buch						activity of Cratva nurvala stem bark extracts in alloxan-induced diabetic rats [53].
Hyssopus officinalis	Lamiaceae	Leaves.	Glycosides, essential oil, sugar, tannins, resins, fats,mucilage, flavonoid glycoside.	Abdominal pain, insomnia, constipation, respiratory tract infections, viral infections and gastrointestinal Disorders.	Antispasmodic, expectorant, sedative, antiviral, astringent, carminative, diaphoretic, tonic and stomachic.	Inhibitory effect Hyssopus officinalis extracts on intestinal alpha- glucosidase activity [54].
Trigonella foenum- graecum L	Fabaceae	Leaves.	Trigonelline, glycosides,flavonoid, saponin, fenugreekine, ascorbic acid.	T2DM, respiratory tract infections, swelling, body pain, stomach pain, piles, dandruff, baldness, breast pain, lungs infection, ulcer and diarrhea.	Anti-inflammatory, tonic and hypoglycemic.	Research and development of indigenous drugs [55].
Smilax chinensis	Liliaceae	Leaves.	Beta sitosterol, oil, diosgenin, smilacin, parallin, sarsaponin resin, tannin, starch, gum, sarsapogenin, sapogenins, and saponins.	Inflammation, cancer and T2DM.	Anti-inflammatory and anti-diabetic.	Antidiabetic activity of Smilax chinensis in alloxan induced diabetic rats [56].
Salvadora oleoides Decne	Salvadoraceae	Fruit, root, seed.	Ethanollic Extract.	Pyorrhea.	Anti-anemic, anti-septic and laxative.	The hypoglycemic activity of ethanollic extract of Salvadora oleoides [57].
Acacia nilotica	Fabaceae	Wood, gum and leave.	Gum arabic, catechin, tannins, mucilage, magnesium, potassium, calcium, arabic acid, malic acid and flavonoid compounds.	Treatment of T2DM.	Astringent and hypoglycemic.	Indusynic Medicine [58].
Aegle marmelos	Rutaceae	Fruits, leaves.	-----	Chronic constipation, dysentery, piles, hyperacidity, abdominal pain and T2DM.	Mucilaginous, antidysentric and antidiabetic.	A study conducted on normal and diabetic rats[59].
Momordica balsamina L.	Cucurbitacea	Fruit and seeds.	Vitamin C and momorcidin.	T2DM, gas flatulence, obesity, trouble, constipation, boils and pimples.	Hypoglycemic, blood purifier and stomachic.	Anti-diabetic and hypoglycaemic effects of Momordica charantia (bitter melon): a mini review [60].
Psidium guajava L.	Myrtaceae	Leaves, fruit.	Ethanollic extract.	T2DM and intestinal worms.	Tonic and anti- diabetic.	Effect of guava (Psidium guajava Linn.) leaf soluble solids on glucose metabolism in type 2 diabetic rats [61].
Syzygium cumini	Myrtaceae	Leave, bark, fruit, nut.	Myrcetin, glucosides, kaemferol, isoquercetin, ellagic acid, anthocyanins, jambolin, jambosine alakloids,	Fever, motion, painful swellings, vomiting, anemia, and T2DM.	Anti-inflammatory and hypoglycemic.	Syzygium cumini extract decrease adenosine deaminase, 5'nucleotidase activities

			and antimellin.			and oxidative damage in platelets of diabetic patients [62].
Curcuma longa	Zingiberaceae	Tubers and rhizomes.	Essential oil, guaiane, turmerol, curcumin, sesquiterpenic ketone, bisabolane, curlone, tumerone, arturmerone, and zingiberone.	Whooping cough, chronic skin disorders, asthma, bronchitis, scabies, irritation, wounds, strokes, bruises, eczema, prurigo and ringworm.	Expectorant, hypoglycemic and blood purifier.	Curcumin and turmeric delay streptozotocin-induced diabetic cataract in Rats [63].
Sesamum indicum	Pedaliaceae	-----	Molybdenum, cobalt, iodine, iron, zinc, calcium methionine, thiamine, niacin, carbohydrates, tryptophan, lecithin, sesamin, sesamolin, phytosterol, and sitosterol.	Cough, inflammations, sexual debility, asthma, thorax complaints, and bleeding piles.	Aphrodisiac, hypoglycemic and anti-inflammatory.	Hypoglycemic effect of a hotwater extract from defatted sesame (Sesamum indicum L.) seed on the blood glucose level in genetically diabetic KK-Ay mice [64].
Ziziphus mauritiana Lam.	Rhamnaceae	Leaves, fruit.	Ethanol seed Extract..	T2DM.	Hypoglycemic.	Hypoglycemic activity of Ziziphus mauritiana aqueous ethanol seed extract in alloxan-induced diabetic mice [65].
Allium cepa	Amaryllidaceae	Leaves and bulbs.	Phytoncides, quercetin, vitamins, allicin, flavonoids, allylpropyl disulfide, essential oil, scordine and fatty oil.	Ear pains, skin diseases and flatulence.	Aphrodisiac and hypoglycemic.	Hypoglycaemic effects of onion, Allium cepa Linn. on diabetes mellitus - a preliminary report [66].
Ficus bengalensis	Urticaceae	Latex, buds, bark, fruits, roots, root and aerial roots.	Triterpine, tannins, friedelin, sitosterol, tigilic acid, quercetin, rutin, waxes, albuminoids and carbohydrates.	T2DM.	Hypoglycemic.	Antidiabetic effect of Ficus bengalensis aerial roots in experimental animals [67].

X. Conclusion

Unlike many other diseases, treatment exists for Type 2 diabetes. Better understanding of Receptor structure and active molecules has helped to develop newer, effective drugs for the treatment. Medicinal Plants are also seemed to be effective in curing T2DM to a great extent.

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