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Mini Review

Anti-Diabetic Drugs and their Effect in T2DM Management

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Abstract

Diabetes mellitus is one of the major health concerns that have attracted the urgent medical attention worldwide. Many evidences has suggested that there is involvement of different signaling pathways and GPCR is involved in the emergence of type 2 diabetes, and targeting them can result in the pivotal development of therapeutic drugs for the treatment of diabetes. Many drugs have developed resistance against the insulin, as research have evidently proved that overcoming such insulin resistance and modifying the abnormal signaling pathways can be a major therapeutic target for the treatment of diabetes. Many anti-diabetic drugs have the ability to provide neuroprotective activity, anticancer and immunomodulatory protection that help to combat the associated risk factors arise due to diabetes. We have focused in this about the effect of different anti-diabetic drugs and to demonstrate how much efficiently these drugs are playing roles in the treatment of diabetes. This study could be helpful in regard of future perspectives to design accurate and best drug for treatment of this metabolic disorder.

Keywords: *Glucagon-like peptide (GLP)-1; Anti-Diabetic Drugs; T2DM Management*

Introduction

An incretin hormone named as Glucagon-like peptide (GLP)-1 having various pharmacological actions followed as high cognitive function, Increased neuroprotection, cardiac protection, high rate of lipolysis, reduced level of hypertension, inhibition of acid release, and exclusively play role iSn protection from high inflammation rate of body. GLP-1 has potent role in providing insulinotropic actions, increased release of insulin, higher β-cell proliferation process, it has also played role in controlling weight gain in type-2 diabetes patients directly involved in control of blood glucose with an glucagnostatic action it processes. As well known benefits of GLP-1 are there but clinically it's not very suitable because it can degraded by an dipeptidyl peptidase-4 enzyme (DPP-4), as many benefits known well known characteristic of GLP-1 is it has half-life of around 2 minutes. In this review, an elaborate discussion is provided in regard to many analogs of GLP-1 which named as Semaglutide, Ittca 650, Efpeglenatide, Albiglutide, Lixisenatide, Dulaglutide and Exenatide. All of these analogs are under ongoing clinical trials. Meanwhile it's also tried to present detailed pharmacology action of these analogs, associated signaling mechanism, and most importantly their pharmacokinetic properties. Major research is going on availability of DPP-IV- resistant analogs of GLP-1. With reference of many research paper it has been known that agonist drugs of GLP-1 has immense capability to cure type-2 diabetes mellitus (T2DM) in comparison of those drugs which are using in clinics currently, as it is also known fact that agonist drugs have not shown side effects such as high weight gain and increased blood sugar [1]. Although many studies has also observed that the biggest contradiction in regard to type 2 diabetes is that it is irreversible but the pathophysiology of many disease are not individually irreversible. It is also the biggest paradox that beta cell loss is known to be irreversible at particular time but it do processes a good capacity for

regeneration. Well an system of multi-organ multi-signal interaction has been created to study pathophysiology of T2DM and to observe it's behavior [2]. However, there are many diseases which are assumed to be cured by targeting mitochondrial biogenesis, as this mitochondrial biogenesis process involves regulation of detoxification, apoptosis, and buffering of ca^{2+} ions, that can be major therapeutic target to cure many diseases that have no cure such as diabetes, Parkinson's disease, cancer, Alzheimer´s Disease, and Huntington´s Disease etc. as mitochondria exhibits an pivotal role because of its efficiency of producing Reactive oxygen species(ROS) and major producer of anti-oxidants [3]. Generally Diabetes mellitus (DM) is generally classified into three main categories as type-I, II, and type-III DM. the drugs that are currently are in use to treat DM have very adverse effects, such as weight gain and edema. peroxisome proliferator-activated receptor (PPAR-γ) agonists is exclusively associated with urinary bladder cancer and fluid retention, many research has been based on giving diabetic drugs in combination instead of following monotherapy will reduce the side effects of anti-diabetic drugs [4]. It has been estimated and predicted that the cases of diabetes globally in 2015 was 415 million and will be reach round 642 million in 2040. Different and numerous types of plasma membrane based glucose transporters as (GLUT1, GLUT2 and GLUT4), are involved in maintaining blood glucose homeostasis along with many neural and hormonal signals as (insulin and glucagon) [5]. It is also known after many studies that diabetes is thought to be an heterogeneous complex metabolic disorder, and it's induction leads to arise of many other diseases as cardiovascular disorder and many neurological disorders also. Many researches has find out important roles of Daidzein and therapeutic applications in cure of insulin resistance and hyperglycemia, soybean and products are known to be abundant or rich source of Daidzein [6]. However, the main cause of occurrence of T2D is the targeted cells which fails to response insulin, many group of MicroRNAs (miRNAs) are involved in regulation of insulin pathway. miRNAs are group of nucleotides, that are non-coding (ncmRNAs), many group of proteins as insulin receptor, IRS 1, IRS 2, type 1A PI3K, AKT2 protein, are involved in insulin transduction so miRNAs are considered to involve in signal transduction pathway and also regulate protein expression level [7]. GPCRs are well known signaling receptors in human body specifically belongs to class A and B family, that also involved in cure of T2D [8]. Type 1 diabetes mellitus (T1DM) is known to be insulin dependent while in case of T2M their is insufficiency or no response to insulin, and pancreatic transplantation is known to become an cure for hyperglycemia or to maintain glucose homeostatic [9] major cause of emergence of T2D is known to take high calorie diet and unhealthy life style infact T2D also results in obesity that leads to hyperlipidemia followed by serious or lethal cardiovascular diseases (CVDs). So, by unravel association between CVDs and T2D can help in production of many potent anti-diabetic drugs [10] research has also revealed that phosphorylation and dephosphorylation of protein has important fundamental role in cell communication, and protein tyrosine phosphorylation has potent role in signaling pathways. And PTP 1B is function as negative regulator of insulin and leptin receptor signaling pathway [11] as observed after many studies that melatonin is involved in the secretion of insulin and plays major role in inducing insulin resistance and glucose intolerance or T2D, so by giving melatonin supplementation susceptibility for T2D can be controlled [12] as by passing years the major health concerned has become the challenge to control pathophysiology of type 2 diabetes and it's associated risk to control the level of hyperglycemia, obesity and mortality rate. Many evidences are nowadays available that have proven the useful effect of microbiota in maintenance of glucose homeostatic in humans studies have been performed on both animal and human models. As science has evolved over a period of time span and extended growth in the field of ayurvedic medicine has shown and put light over many productive therapeutics for diabetes control and one of them is the berberine (BBR), and it is a plant based alkaloid known to be isolated from the *Berberis aristata* and *Coptis chinensis* (Huanglian), and it is also known to be useful since ancient times is a basically an anti-diarrhoeal medicine and is well known for its potential as a anti-diabetic drug as it plays major role in the lipid metabolism and browning of adipose tissues. Role of gut microbial dysbiosis has been extensively studied and observed in regard for controlling rate of diabetes population increase [13]. Diabetes known to believe as one of the most prevalent disease in the world and it is known to arise as a combination of disordered state and also causes decreased and abnormal production of insulin which might cause heart, kidney complications and along with that neural disease that brings notable attention to found cure for diabetes. Many research articles have been published and shown that the abnormal TGF-beta signaling pathways along with the dysregulated autophagy are responsible for the initiation of diabetes along with many complicated conditions such as neuropathy and cardiopathy. Resveratrol helps in the blocking the TGF-b/SMAD and extracellular signal-regulated kinase (ERK)1/2 signaling that causes diabetic neuropathy [14]. Sirtuin 1 are molecules that belongs to the family of Sirtuins, it is also known as or called as the NAD-dependent deacetylase that are majorly analysed and ob-

served in the bacteria. Past studies on sirtuins have shown that there are seven types of sirtuins are present in case of humans and are localized in the nucleus and cytoplasm area of body. Major role of Sirtuins are seen in the case of severe metabolic disorders such as type 2 diabetes, they are involved in the deacetylation of many uncoupling proteins and PPARG co-activator-1 α (peroxisome proliferator activated receptor γ co-activator 1 α). Main uncoupling protein that plays major role in the site of adipose tissue is the uncoupling protein 2 (UCP2) that is known as the negative regulator in regulation of insulin and other factor behind the glucose production in the liver and for maintain proper pathway of gluconeogenesis is the PPARG co-activator-1 α [15]. Research has investigated and confirmed that Diabetes is fast emerging lifestyle based metabolic disorder but according to current scenario there is an urgent need to produce some novel drug or management skills to deal with this diabetes pandemic. Hydroxytriazene is a compound that is bidentate ligand and have attached alpha hydroxyl group that is very much related to diazo and azo group and also has major analytical application as they form chelate complex incorporation with many transition elements. As many attempts have been made for better management of the Diabetes but recent studies shown Hydroxytriazene based α-glucosidase and α-amylase enzymes inhibition can be a useful method and might result as an important tool on this basis docking studies have also performed to show complex, activity and structure based relationship of following compounds. Along with that antioxidant and anti-inflammatory activities of hydroxytriazenes, have also studied [16]. the process of secondary metabolism has resulted in the formation of many compounds that are usually plant based derivatives known as Polyphenols that in itself is a very wide group that is uniformly and ubiquitously distributed in the plant kingdom and have varieties of applications such as the bacteria, fungi and viral infections protection. Many immunomodulatory effects of myricetin have been known till now that are involved in many functions such as antidiabetic, anticancerous and antioxidant roles in human [17]. Diabetes is a disorder that is believed to arise due to the failure of pancreas capacity to produce insulin or it is also known to caused due to inability of body tissue to take insulin or become insulin resistant. Pterostilbene (PTS) (trans-3,5-dimethoxy-4-hydroxystylbene) is derived and produced by the *Pterocarpus marsupium* (leguminosae) tree, it is known as a natural antioxidant also designated or named as the Indian kino or bijasar plays major role in the management and control of diabetes by controlling and helpful in properly managing level of glucose in the body. As diabetes is known as the severe metabolic disorder and also cause crucial complications in T2D patients and one of that is Hearing loss. Diabetes Mellitus (DM) is responsible for causing hearing loss in VIII nerve, cochlea and Temporal bone. DM is also involved in the arise of blindness, cause kidney malfunction that results in cascade of reactions initiates formation of free radicals in the body and also causes heart vessel associated disease [18] in recent findings and surveys it has been analyzed that DM have increased to the level of four times in India in comparison to the level on which it was before, and it's increasing prevalence is worldwide is considered as a boom. Asian diabetes is considered to play significant role in the rise of diabetic pandemic worldwide, and in series of 90% cases of diabetes major proportion is of type 2 Diabetes. Worldwide china and India have becomes the two major epicenter of type 2 diabetes and have contributes to significant proportion for the rise of this pandemic. *Ficus krishnae* CDC (Moraceae) is known to belong from India, it has been used in many medicines and many part of this useful plant is used to cure many kind of ulcers and inflammation of liver also have potent and important antihyperglycemic activity [19] as evidences shows amongst between different kinds of diabetes type 1 and type 2 diabetes are more chronic and usually discussed in many literatures. After analyzing different aspects of diabetes major factors behind the arousal of diabetes is family history, ethnicity, gestational diabetes, obesity and overweight, physical inactivity and smoking are bound to increase risk of diabetes [20].

Conclusion

As this review will help in showing the efficacy of the various anti-diabetic drugs and also discusses about the complications associated with such drugs. And if saying precisely daidzein helps in lowering the level of insulin resistance, and not only this it also ameliorates the inflammation level occurs in body and improves plasma lipid profile during the course of diabetes will also reliefs the complications arises in diabetes. After many investigations it has been concluded that daidzein is active and functional in it's aglycone form and observations have also claimed that it will only be active when it's glycosidic bonds have been cleaved. fermented soybean is known to be active and most important source of daidzein in the bioactive form and also serves the important many isoflavones because the process of fermenta-

tion break down the glycosidic bonds in the drug. Many literature have shown the evidences that there is strong relation of daidzein and T2D as consuming it lowers the risk of diabetes [6]. A review published in 2006 has mentioned or one can say proves that GPCRs, are crucial target for the cure of T2D as GPCRs are ubiquitously present in the body and are of major involvement in various signaling pathways. As in course of diabetes many tissues and cells of the body are prominently involved and played useful role to maintain the level of glucose in the body along with that there is also constitutive importance of pancreas, hepatic and adipose tissue involvement in the procedure. As research has analyzed that many kind of unknown GPCRs express prominently in these following mentioned tissues. And these kinds of GPCRs are involved in the glucose regulation and if these GPCRs are activated will helps in the risk of having T2D [8] as research conducted over the many decades have revealed that many miRNAs have been involved in the regulation and proper signaling of the insulin regulation pathway, and targeting or studying the action mechanism of such small miRNAs will be of immense importance in regard to cure of T2D in accordance with the future perspective. As many miRNAs have the potential and efficacy to initiate and maintains the signaling cascade required for proper insulin regulation in the body, and past research over the miRNAs have indicated that many insulin resistance tissues involving different kinds of protein cascades thus helps in finding out or diagnose if one has T2D or not. And miRNAs also can play highly useful role in carrying out upregulation and required downregulation of many proteins and their expression to adjust level of insulin resistance [7]. As published data says that many deaths occurred because of diabetes usually associated with complications one has to face during diabetes. Regeneration and repair capacity of the stem cell has grabbed the special attention in the way of helping out as a therapeutic as many cell based therapies can be used as a treatment of the disorder because of the pluripotent and multipotent nature of the stem cell, as extensive studies should require [9] diabetes is a multifaceted disorder and due to insulin resistance during diabetes increases the oxidative stress, dyslipidemia and hyperglycemia which results in the greater chances of cardiovascular attack in diabetic patients. To find out cure for the type 2 diabetes insulin sensitizers are of more importance as many anti-inflammatory and anti-oxidants could also enhance activities of Akt, NO, GLUT4 and PI3K receptors. Diabetes interrupted the insulin induced glucose uptake and also affects negatively vasodilation and endothelial cells function that leads to cardiomyocytes to compromise their function which ultimately results in the atherosclerosis, hypertrophy and fibrosis. Many scientists have suggested that the therapeutic for diabetes should better be designed in accordance with that of the metabolic rate of the diabetic patient [10]. Protein Tyrosine Phosphatase 1B (PTP 1B) is ins spotlight to helps in management of the diabetes and also to control the obesity emerging rate, research says both of it's artificial and natural kind of compounds helps in the cure of T2D. Difluoromethylene phosphonate is a synthetic compound and have extensively high Ki value, along with that many natural kind of PTP 1B compounds do exist play important role to control diabetes, such as The *Schisandra chinensis*, *Flemingia philippinensis* and these compounds are available at the affordable rate and possesses the prominent IC_{50} value 2.36. In the way of becoming the therapeutic for the diabetes many research has focused only on analyzing the inhibitors activity over the catalytic and secondary binding site of the PTP 1B compound. Inhibitors of PTB 1B should be having high efficacy of inhibition and having good physiochemical properties with almost minimum side effects [11]. Studies conducted over the use of Circadian system to decrease the rate of increasing diabetic patients have played an productive role and also be effective in decreasing the insulin resistance level and hyperglycemia index. Many experiments conducted on the animal models have shown that giving melatonin supplementation to diabetic mouse model results in the positive regulation of the glucose homeostasis and also helps in weight reduction and will also recommend hormone to be used in clinical trials and might serve function as a therapeutic. IP3- signaling pathway is induced by the melatonin secretion in the body and also helps in betterment of the beta cells function that are majorly involved in insulin release [12]. Autophagy andTGFb1/SMAD signaling cascades are of immense importance in the way of therapeutic against the diabetes, as proper signaling pathways helps in the maintenance of beta cells function [14]. Myricetin have the anti-cancer and anti-diabetic activity and also work as a efficient anti-oxidant, it serves function as a nutraceutical and is originally a flavonoid present in many foods [17]. *Ficus krishnae* is the ultimate and important source of compounds such as two phytosterols (CA+24-MCA), that have anti-diabetic activity, helps in increasing the beta cell population and enhance proper release of insulin from beta cells present in pancreas [19].

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