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Novel Therapeutic Advancements in Type 2 Diabetes

Review Article

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Abstract

Type 2 diabetes mellitus (T2DM) is a metabolic disorder of the endocrine system and its prevalence has increased at an accentuating rate in the past years. Its growing prevalence is a matter of concern as it is one of the major contributing factors for the mortality and morbidity due to cardiovascular diseases and related ailments. Current treatments involve the use of sulfonylureas, metformin, d-phenylalanine analogs, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors as mono or combination therapy. However, the current treatments are accompanied with undesirable side effects that could be reduced through novel advancements. Moreover, not only the prevalence but the factors that trigger the development of T2DM are also increasing which brings about the need to develop new drugs in order to treat the same. In this review, authors have discussed some recent novel advancements in the current treatment, novel drugs that are at different stages of discovery and development for the treatment of T2DM and novel targets aiming which we could develop new drugs with enhanced therapeutic efficacy and reduced side effects. Additionally, the authors have attempted to discuss the other novel therapeutic uses of the currently available drugs.

Keywords: Re-purposing of the drug; Off-label use of drug.; GLP-1; DPP-4

Introduction

Diabetes mellitus is a cluster of metabolic disorders characterized by hyperglycaemia. Decreased insulin secretion and insulin action could be the reason for the development of this disease associated with the endocrine system. Symptoms of this disease include polyuria, polyphagia, polydypsia, weight loss, blurred vision and sometimes may lead to impairment of growth or increased susceptibility towards certain infections. Uncontrolled diabetes may also lead to ketoacidosis and non-ketonic hyperosmolar syndrome.

Types of diabetes and its prevalence

There are mainly two types of diabetes- Type 1 & Type 2: Type 1 diabetes is an autoimmune disorder and caused by auto-immune destruction of β-cells leading to marked reduction in insulin production or could be idiopathic, where the etiology is not known.

Type 2 diabetes/diabetes mellitus (T2DM) is more prevalent than type 1 diabetes and is caused mainly due to insulin resistance in cells or relative deficiency of insulin secretion that is inadequate to perform its function. This abnormality of insulin secretion and action leads to hyperglycaemia and is underlying for several years before showing any symptoms in the patient. Age, obesity and lack of exercise are often contributing factors for this disease [1].

According to the Diabetes Atlas (Ninth Edition 2019) published by Indian Diabetes Federation (IDF), there are currently 463 million people suffering with diabetes and the number is going to accentuate to 578 million and 700 million by 2030 and 2045 respectively. India

was found to be home to 72 million of adults with diabetes, being the second largest worldwide. In the South East Asia region, India has the largest diabetes mortality rate with more than 1 million deaths due to diabetes and related complications [2].

Inculcation of some habits for a healthy lifestyle is a valuable preventive measure, but what about those who already have this disease. There are so many factors that develop this disease and therefore, we need drugs that target those factors. Additional factors that could be the reason for development or advancement of this disease are being discovered at a remarkably rapid rate, and unknown factors that may be reason are yet to be discovered. This leads us to the need to develop new drugs for the same. Moreover, a combination of drugs that targets over one cause at a time is being researched and developed to meet the needs of patients. Thus, in this article, we will discuss the drugs that are now available to treat T2DM, drugs that FDA has recently approved, and novel drugs that are being developed.

Target receptors and novel drugs for T2DM

• **Sulfonylureas:** They are being used since very long to treat T2DM. Carbutamide was the first drug under this class but was withdrawn due to its side effects on bone marrow [3]. The first generation drugs under this class were tolbutamide and chlorpropamide which posed cardiovascular risks in patients and showed incidence of hypoglycaemia. Overcoming all the side effects, second generation drugs like gliclazide, glipizide, glibenclamide and glimepiride are now being used to successfully treat T2DM [3] (Figure 1).

• **Meglitinide or D-phenylalanine analogs:** These include insulin secretagogues like Repaglinide and Nateglinide that are used to control post-prandial hyperglycaemia without causing hypoglycaemia between the meals in diabetic patients [3,4]. Mitiglinide is a new addition in this class. Both classes have similar mechanism of action that is explained in the figure given below [5] (Figure 1).

• **Metformin:** Metformin (N, N'- dimethyl biguanide) is used worldwide as a drug for the treatment of T2DM [6]. It shows its antihyperglycaemic effect by increasing the insulin sensitivity of peripheral tissue and inhibiting hepatic gluconeogenesis [7]. It also inhibits the mitochondrial complex 1 that results in disruption of cAMP and protein kinase A signaling in response to glucagon [8]. There is now evidence that metformin could be used for the treatment of other related diseases like neurodegenerative diseases, cancer and cardiovascular diseases and also in the treatment of Polycystic Ovarian Syndrome [9,10]. Thus, research and trials are being conducted to understand these novel uses of metformin. Given below are the novel advancements in metformin.

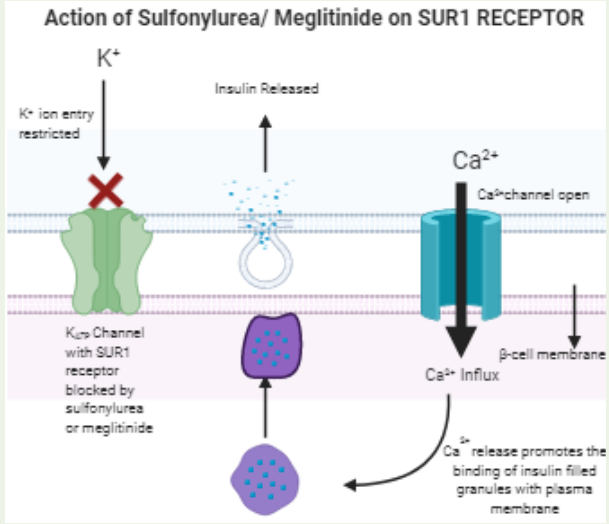

Figure 1: Mechanism of Action of Sulfonylureas and D-Phenylalanine Analogs.

Metformin in the treatment of Cancer

The cross talk (interaction between signaling pathways forming complex networks) between heptahelical G-Protein Coupled Receptor (GPCR) signaling system and insulin/insulin-like. Growth Factor-1 (IGF-1) receptor plays a significant role in the regulation of various physiological functions and a number of anomalous processes like cardiovascular and renal abnormalities in obesity, T2DM and metabolic syndrome. Thus, these abnormalities could be considered as a trigger for the growth of cancer cells. GPCRS and similarly derived agonists have been found as autocrine/paracrine growth factors for solid tumors in pancreas, breasts, colon and prostate gland. At cellular level, insulin coordinates with the agonists of GPCR in stimulating mitotic signaling, DNA synthesis as well as proliferation of pancreatic cancer cells.

This crosstalk is dependent on the mammalian Target of Rapamycin (mTOR) complex one (m TORC 1) that is inhibited by AMPK at multiple steps which leads to the disruption in the crosstalk between the two receptors, thus leading to inhibition of growth of cancerous pancreatic cells. Metformin has the ability to stimulate the AMPK, thus, could take part in inhibiting the crosstalk. In recent studies, metformin showed a significant reduction in the growth of pancreatic cells heterografted in nu/nu mice. Also, recent epidemiological studies show that metformin can be attributed for reducing the risk of pancreatic, breast, colon as well as prostate cancer as it prevented the growth of breast and p53-/- colon cancer cells in animal models. Thus, metformin is being considered as a new therapeutic agent for treating the cancers mentioned above [11].

• **Thiazolidinedione(PPARγ agonists):** PPARγ is the factor involved in regulating the expression of genes involved in glucose and lipid metabolism. Thiazolidinediones, being agonists of this receptor help in regulation of insulin sensitivity, manage the uptake and storage of glucose and lipid in the body [12] (Figure 2). They also show anti-inflammatory and anti-atherosclerotic actions [13]. Unfortunately, when these drugs are used alone, they cause undesirable side effects, such as weight gain, edema and anaemia [14].

Troglitazone was the first drug under this class that was soon withdrawn due to occurrence of severe hepatotoxicity in patients [15,16]. Rosiglitazone has also been withdrawn from India and Europe as it posed increased risk of myocardial infarction in patients [17]. Pioglitazone was withdrawn from India due to incidence of bladder cancer in patients consuming it but is now sold with a boxed warning

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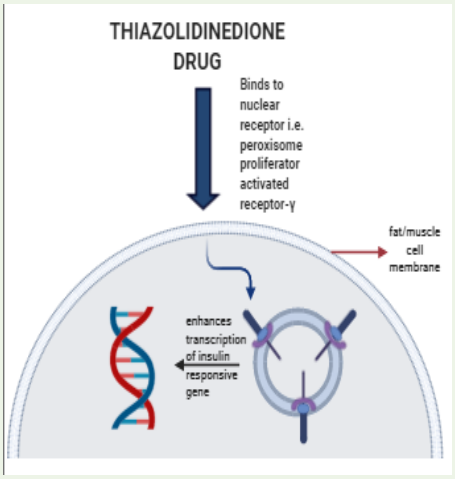

Figure 2: Mechanism of action of Thiazolidinediones.

[18]. Lobeglitazone is being used in the treatment of T2DM and it has also shown promising results in clinical trials for its effectiveness in the treatment of non-alcoholic fatty liver disease in diabetic patients [19].

Drugs Currently in Clinical Trial (Table 1)

• Saroglitazar Mg- It is a dual PPAR α/γ agonist with greater effect on the α-subtype. It was approved in 2013 in India for the treatment of diabetic dyslipidaemia and hypertriglyceridaemia in patients not receiving any statin therapy for the same. In 2020, it was approved to be used as an ad-on to metformin in the treatment of T2DM and also for non-cirrhotic non-alcoholic steatohepatitis in India [20].

Novel Advancements (Table 1)

• **Benzylidene Thiazolidinediones Derivatives as partial PPARγ agonists:** The already available thiazolidinediones (TZDs) are full agonists of PPARγ receptors and are bound to the TZD nucleus through hydrogen bonding. Aforementioned, these full agonists show various side effects and thus, new agonists are being researched that have the same or better therapeutic effects with fewer side effects.

One such class serving the purpose mentioned above is of novel 5-Benzylidene Thiazolidin- 2,4dione Derivatives (BTZD). This novel class of compounds is selective agonists of PPARγ receptor with partial binding affinity because these derivatives bind through hydrophobic bonds with the ligand binding pocket in the TZD nucleus. BTZD have been formed by making different substitutions at the nitrogen atom present in the TZD nucleus. Eleven derivatives were formed by this procedure and were tested on GAL-4 PPAR chimeric receptors and were expressed in temporarily transfected HepG2 cells [13]. Among these 11 derivatives, only 1a and 1i were shown to have weak to moderate activity towards PPARγ at a concentration of 5 μM and 25 μM. Further five analogues of 1a and nine analogues of 1i were tested using the same procedure for their activity and among these, only 3a showed the desired activity.

Thus, 1a, 1i and 3a were discovered as partial agonists of PPARγ and their activity was found to be weak to moderate using Surface Plasma Resonance. Pioglitazone 1a, 1i and 3a were administered in Streptozotocin-Nicotinamide (STZ-NA) induced diabetic rat at a dose of 36mg/kg and the rat models showed improvement in hyperglycaemia and prevention in the increase of HbA1c in comparison to the rats being given placebo. Moreover, the histopathological damage to tissues in pancreas and liver caused by STZ-NA induced diabetes was also restored in the ones receiving the drug dosage. 1a, 1i and 3a are found to be cytotoxic at a concentration of 100M but not at their effective dose concentration. Based on these observations, the scientists have found this new class of substituted thiazolidinediones with partial affinity as potent drugs for T2DM [13].

• **INT131:** Diaryl sulfonamides are a novel chemical class that acts as selective PPARγ Modulators (SPPARMγ). Studies for its structure activity relationship and pharmacological profile led to the selection of INT131 as a potent partial agonist under this class. INT131 is a non-thiazolidinedione SPPARγM that binds to the same binding pocket as thiazolidinediones but has unique binding site and interacts with the receptors at sites different from the interaction sites of TZDs. This distinction in binding leads to alternative conformational change in PPARγ, thus, leading to difference in gene transcription caused by INT131 and TZDs. This enables INT131 to retain its anti-diabetic activity and have minimal side effects, if any. INT131 has higher affinity for PPARγ than rosiglitazone and pioglitazone. Moreover, it has greater than 1000 fold selectivity for PPARγ over PPARα and PPARδ. INT131 has successfully completed pre-clinical studies and has proved to be more potent than the TZDs full agonists in lowering serum glucose, insulin, and triglycerides and also improved glucose tolerance. It also increased the levels of adipokine adinopectin and improved the level of adinopectin, otherwise reduced in obesity and T2DM and acted as a mediator for insulin sensitivity and anti-inflammatory effects of PPARγ. It was well tolerated by animals in pre-clinical studies without depicting any toxicity and also demonstrated lower risk of carcinogenicity in comparison to full PPARγ and dual PPARγ/α agonists. It was also well tolerated in patients in Phase 1 and 2a clinical trials and showed efficient anti-diabetic activity which led to the conduction of its Phase 2b trials in which it is being compared with pioglitazone to test its SPPARγM activity [21].

• **α- Glucosidase Inhibitors:** α-Glucosidases are a group of carbohydrate digesting enzymes. The α-glucosidase inhibitors act by competitively inhibiting these enzymes as well as α-amylase so that the absorption of sugars from the gut is delayed [22]. This delay grants the body time to produce enough amount of insulin to digest the carbohydrates ingested by the person [17]. However, a recent clinical study conducted on healthy subjects has shown that the medicinal effects of α-glucosidase inhibitors may also be based on metabolic effects of colonic starch fermentation [23]. They decrease both post prandial hyperglycaemia and hyperinsulinaemia and may increase the sensitivity towards insulin [22]. They have also been found to reduce the stress on pancreatic β-cells by promoting the release of incretins such as GLP-1 [17, 22].

Drugs under this class that are sold in the market are- Acarbose, Voglibose and Miglitol. Among these, Acarbose is the most widely prescribed α-glucosidase inhibitor [24]. The already present

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Table1: Summary of Current treatments and novel advancements.

S.NO.	Class of Drug	Target Receptor	Example	Status
I.	Sulfonylureas	SUR1	Gliclazide, Glipizide, Glibenclamide and Glimepiride	Approved by FDA[33]
II.	Meglitinide or D-Phenylalanine Analogs	SUR1	Repaglinide and Nateglinide	Approved by FDA[34]
III.	Thiazolidinediones	PPARγ	Troglitazone and Rosiglitazone	Withdrawn from the Market[15,17]
			Pioglitazone	Sold with a boxed warning in India[18]
			Lobeglitazone	Used for treatment of T2DM[19]
		Dual PPARα/γ agonists	Saroglitzar Mg	Approved in India[20]
	Benzylidene Thiazolidinediones Derivatives	Partial PPARγ Agonists	1a, 1i and 3a derivatives under consideration.	Under research [31]
	Diaryl sulfonamides	Selective PPARγ modulator	INT131	Under Phase 2b clinical trial[21]
IV.	α glucosidase inhibitors	α glucosidase enzyme	Acarbose, Voglibose, Mitigol	Approved by FDA[17]
			(R)-4- fluorophenyl-1H- 1,2,3 triazole bromide.	Under Research[26]
			Substituted 3-aryl coumarins derivatives	Under Research[27]
V.	GLP-1agonists		Adlyxin (Lixisenatide) Injection	Approved by FDA in 2016[33]
			Soliqua (100/33-Insulin glargine and lixisenatide) injection	Approved by FDA on November 21,2016[33]
			Bydureon BCise	Approved by FDA in 2017[32]
			Ozempic (Semaglutide) Injection	Approved by FDA in2017[33]
			Rybelus (Semaglutide) Tablets	Approved by FDA in 2019[33]
			LY2944876	Was in Phase 2 clinical trial in 2016[34]
			LY3298176 (tirzepatide)	In clinical trials[28]
			Abextide 2	Under Research[36]
VI.	DPP-4 Inhibitors	Act on DPP-4 enzyme	Sitagliptin, Vildagliptin and Saxagliptin	Approved by FDA[17]
			Galangin	Pre-clinical studies conducted[38]
			ZY15557	Pre-clinical studies conducted[39]
			Evogliptin	Under clinical development and received approval in South Korea[40]
VII.	SGLT-2 Inhibitors	SGLT-2 PROTEIN	Dapagliflozin, Empagliflozin and Canagliflozin	Approved by FDA[42]
			Steglatro and Segluromet.	Approved by FDA in 2017[33]
			Remogliflozin Etabonate.	Completed its Phase 3 clinical trial and approved by the Health Regulatory Authority of India[43]
VIII.	Combination drugs targeting DPP-4 and SGLT-2 receptors.	Target DPP-4 enzyme and SGLT-2 protein	Glyxambi	Approved in 2015
			Qtern and Qternmet XR	Approved in 2017 and 2019 respectively[45]
	SIRTUIN-1			Agonists for it are being researched[46]
	Obeticholic Acid			Pre-clinical studies conducted[47]
	G-Protein Coupled Receptor			Preclinical and clinical studies conducted. Synthetic agonists TAK-875 (83) and AM837 under development[48].

α-glucosidase inhibitors are known to produce gastrointestinal side effects and have low efficacy with high IC_{50} value [25]. Thus, there is a need to search novel compounds that could overcome these problems. Some of the novel compounds are discussed below-

- **(R)-4-Fluorophenyl-1H-1,2,3Triazolebromide:** This chemical compound and its derivatives (8a-n) were synthesized using commercially available S-ethyl lactate via modified Chiron approach. Screening of all of the above mentioned compound and its derivatives depicted effective inhibition of α-glucosidase enzyme with lesser IC_{50} value in comparison to the standard Acarbose. *Saccharomyces cerevisiae* α-glucosidase was used to conduct the molecular docking study of this novel compound and its derivatives. The studies showed that 1, 2, 3-triazole ring in (R)-4-fluorophenyl-1H-1, 2, 3-triazole derivatives was responsible for the inhibitory activity towards α-glucosidase by this novel compound and fluorine is the best substituent on its phenyl ring in order to carry out the same [26].

- **Substituted 3-aryl coumarins derivatives:** 3-arylcoumarin belongs to the class of naturally occurring compounds- arylcoumarin. Its derivatives were synthesized using microwave radiation heating.

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The derivatives 11, 17 & 35 formed by various substitutions in 3-arylcoumarin are of our interest as they show anti-diabetic activity through their inhibitory effect on α-glucosidase enzyme during *in vitro* studies. During *in vivo* hypoglycaemic assay, these derivatives reduced the glucose levels in Streptozotocin (STZ) diabetic mice compared to healthy mice. Further chronic experiment of these three derivatives led to the observation that derivatives 17 & 35 were more effective than 11 in preventing body weight gain in hyperglycaemic mice and they also reduced postprandial hyperglycaemia in STZ-mice. Thus, based on all the experiments conducted, 17 & 35 were found out to be equipotent to glibenclamide in their anti-diabetic effect. Keeping all the factors in mind, the derivative 35 was concluded as the potent novel compound that offered potential drug design concept and anti-diabetic activity [27].

• **Glucagon-like Peptide- 1 (GLP-1) analogues:** GLP-1 receptors are a member of class P family of G-protein coupled receptor that are expressed in β-cell of pancreas, various cell types of gastrointestinal tract and neurons present in the nervous system [28]. These receptors secrete an incretin hormone named GLP-1 after the intake of glucose that promotes insulin secretion from pancreatic β-cells and decreases the secretion of glucagon from pancreatic α-cells. Besides this, it also delays gastric emptying, prevents β-cell apoptosis or promotes β-cell proliferation as well as reduces appetite [29]. It has also been observed to exhibit other pharmacological functions like increased cognitive activity, decrease in cardiovascular risks etc. [37]. The glucose dependent action of GLP-1 seems promising in avoidance of the unwanted weight gain [30]. Although, a major problem posed by this incretin is its short half life of (2-3 min) and the degradation action of dipeptidyl peptidase-4(DPP-4) enzyme on it [31]. Thus, GLP-1 analogs were developed that have prolonged action in *in-vivo* conditions and show resistance towards degradation by DPP-4 enzyme [29] (Figure 3).

Drugs Approved by FDA (Table 1)

a. Bydureon BCise- It is an injectable suspension prepared by Astra Zeneca. It has to be administered once a week and was approved by the FDA in 2017. This new formation of bydureon is an incretin mimetic to improve glycaemic control and has the added benefit of weight loss. Unlike other agonists available, it has a microsphere delivery system that ensures consistent release of adequate amount of exenatide. However, in its clinical trials, it was found out that it produces hypoglycaemia if co-administered with insulin. It may also produce itching or nodules at the site of injection [32].

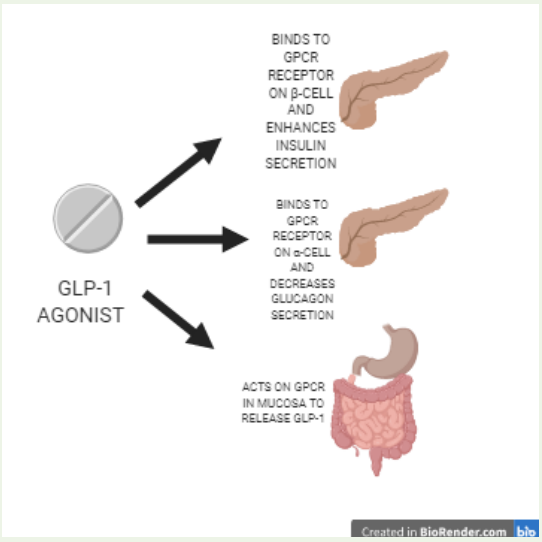

Figure 3: Mechanism of Action of GLP-1.

b. Rybelus (Semaglutide) Tablets- FDA approved this drug on September 20, 2019. The company that proposed this drug is Novo Nordisk. It is an oral GLP-1 receptor agonist [33].

c. Ozempic (Semaglutide) Injection- It was approved by FDA on December 5, 2017, and was prepared by Novo Nordisk. It is a weekly GLP-1 analogue [33].

d. Adlyxin (Lixisenatide) Injection- It was approved on July 27, 2016, and its parent company is Sanofi. It needs to be administered once daily and is prandial GLP-1 agonist [33].

e. Soliqua (100/33-Insulin glargine and lixisenatide) injection- Sanofi made this combination of drugs. It is prescribed to be used as adjunct to diet and exercise in order to enhance glycaemic control. It was approved by FDA on November 21,2016 [33].

Drugs That Are Currently in Clinical Trial (Table 1)

a. LY2944876: This drug was in Phase 2 of the clinical trial in 2016. The company that is conducting its trial is Eli Lily. This drug is given through injection under the skin. It is an oxyntomodulin analog. It belongs to the class of antihyperglycaemic and obesity therapy[34].

b. LY3298176 (Tirzepatide): This novel drug belongs to a new class of dual receptor agonists that target GLP-1 as well as Gastric Inhibitory Peptide (GIP). This drug is a fatty acid modified peptide. It is required to be given subcutaneously once a week. Even a clinical trial was conducted to compare its therapeutic effects to placebo and Dulaglutide (https://clinicaltrials.gov/ no. - NCT02759107). The results of this clinical trial came out to be very promising as it showed effective glycaemic control and improvement in body weight. Moreover, its chronic administration helped in decreasing body weight and food intake. The side effects of this drug are mostly gastrointestinal, such as vomiting, diarrhoea, abdominal distension etc. However, all these side-effects are dose dependent with mild to moderate severity [28].

Novel Advancements (Table 1)

a. Novel GLP-1 gene delivery complex- GLP-1 receptor agonists have come out as a potent class of drugs for the treatment of T2DM. However, their short half-life (<5 min.) and rapid clearance rate limits their therapeutic efficacy [31]. To deal with this shortcoming, scientists have developed oral delivery of therapeutic DNA by antibody. In this, human IgG1 (hIgG1) – Fc-Arg/ pDNA complex was prepared by electrostatic complexation of expression plasmid and various ratios of the positively modified Fc fragments of an antibody which targets FcRn receptor (a neonatal receptor). The bio-distribution and anti-diabetic action of the complex was examined either in Balb/c mice or $Lep_{db}/_{db}$ mice.

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GLP-1 gene delivery system on the cationic hIgG1-Fc-9Arg showed increased half-life, less immunoactivity and superior bio-activity than simple GLP-1 analogs. Thus, this delivery system could be a favourable approach for using GLP-1 [35].

b. Abextide 2-Exendin-4 is a peptide that is extracted from the saliva of Gila monster and 53% of its amino acid sequence is similar to the mammalian GLP-1 and shows resistance to degradation by DPP-4 enzyme. Though commercially available exenatide overcomes almost all the drawbacks of GLP-1, it requires twice-daily administration due to its rapid clearance rate. In order to overcome this problem, the molecular size of this protein drug was increased by using albumin as a drug carrier. Albiglutide, an exendin-4-albumin analog is a fusion protein that has been made using this approach and is very effective but the fusion protein is hard to prepare and store. Thus, there emerged a need to synthesize analogs of exendin-4 that bind covalently with albumin and have a greater half-life. Using Evans Blue dye, they initially prepared Abextide that has similar *in vivo* function as exendin-4 in healthy BALB/c mice and in diabetic model of rodents. However it was prone to hydrolyzation which made it lose its therapeutic efficacy. Thus, they synthesized a more stable maleimide modified Evans Blue dye to bind with Cys-40 in order to make Abextide 2 that was stable in both powder and solution forms at room temperature and it was found to be more effective than Albiglutide in decreasing glucose levels in db/db mice [37].

• **Dipeptidyl Peptidase-4(DPP-4) Inhibitors (Table 1):** DPP-4 is a protease enzyme that is made up of 766 amino acids. Its degradation action on GLP-1 leads to decrease in the concentration of these incretins in the body due to which there is a rise in blood sugar level. Thus, inhibitors of DPP-4 enzyme were considered as a novel treatment for T2DM. DPP-4 inhibitors are orally active drugs whose bioavailability is greater than 80% when taken orally and are capable of reducing the release of DPP-4 enzyme by more than 90% for about 24 hours. They are also capable of inducing the release of GLP-1 and GIP, because of which the load on pancreatic β-cells to secrete insulin for glucose utilization is reduced. Thus, they help in preventing oxidative stress in pancreatic β-cell, which is one of the main reasons for β-cell apoptosis in patients with T2DM. They help in enhancing the β-cell activity and this is evident as the release of insulin is increased. They are capable of reducing the HbA1c by 0.7 to 0.8% and play a major role in controlling fasting and post-prandial hyperglycaemia. They also reduce the secretion of glucagon which ultimately prevents hepatic glucose production in patients with T2DM [37]. Sitagliptin, Vildagliptin and Saxagliptin are some FDA approved drugs under this class that are being used for the treatment of T2DM [17].

Drugs under Development (Table 1)

a. Galangin: Skeletal muscles are responsible for about 40-50% insulin dependent glucose uptake. However, insulin resistance due to T2DM leads to abnormal glucose levels and reduction in the mass of the skeletal muscles in our body. There is no combination or mono therapy that targets improvement in skeletal muscle health along with restoring normal glucose levels. It has been shown that exercise leads to reduction of DPP-4 enzyme levels in our body and this leads to improved skeletal muscle mass. Thus, it was concluded that the inhibition of DPP-4 could lead to improvement in skeletal muscle health as well as restore glucose homeostasis. For the same purpose, using molecular docking simulations the efficacy of a natural flavanoid named galangin (3, 5, 7 trihydroxyflavone) has been studied and it has shown to bind to the DPP-4 enzyme in order to inhibit it. *In vitro* studies showed that galangin inhibits DPP-4 in a dose dependent manner.

Sulforhodamine B (SRB) assay was used to demonstrate its effect on rat L6 skeletal muscle cells. Both alone and in combination with insulin, galangin demonstrated proliferation of differentiated skeletal muscle cells and also reduced glucose levels in skeletal muscles better than when the cells were treated alone with insulin. Reduction in glucose levels in skeletal muscles also indicates overall reduction in plasma glucose levels as skeletal muscles constitute major part of the body. Thus, galangin seems a promising novel compound for the treatment of T2DM along with improving the skeletal muscle health in body affected due to T2DM [38].

b. ZY15557: It is a competitive inhibitor of DPP-4 enzyme and has a longer half-life than the currently available DPP-4 inhibitors. It is highly selective for DPP-4 and relatively less effective against DPP-8 and DPP-9. *In vitro* ZY15557 inhibited serum DPP-4 activity in rat, mice, dog, monkey and humans. In C57 mice and Wistar rats, it even increased the of GLP-1 and insulin levels. In db/db mice it also reduced the extremely high level of insulin and the level of glycated hemoglobin (HbA1c). In the hyperlipidaemia phenotype of db/db mice, it reduced hepatic cholesterol accompanied with decrease in hepatic oxidative stress. Thus, it is concluded that ZY15557 is an effective competitive inhibitor of DPP-4 enzyme with accentuated half-life and sustained action [39].

c. Evogliptin: It is a piperazine derivative and competitively inhibits the DPP-4 enzyme. In preclinical studies, it has shown to improve the insulin sensitivity in high fat diet- fed mice, increased the neogenesis and multiplication of β-cell in Streptozotocin induced diabetic mice and delayed the inception of diabetes in young leptin receptor deficient db/db mice. Based on these promising results in animal studies, evogliptin is now under clinical development and received its first approval in South Korea in October 2015 for glucose control in diabetic patients [40]. It acts in a dose dependent manner and has a sustained action [41].

• **Sodium-glucose co-transporter 2(SGLT2) Inhibitor:** Kidneys are known to have a major role in maintaining glucose homeostasis through gluconeogenesis as well as glucose reabsorption. SGLT-2 plays a major role in reabsorbing glucose from the glomerular filtrate and is responsible for the reabsorbing about 90% of the filtered renal glucose through the brush border cells in the proximal convoluted tubule.

Phlorizin is a naturally occurring glucoside obtained from the root bark of fruit trees and is responsible for the origin of the SGLT2 inhibitors. In 1950s, a study was conducted in which phlorizin blocked the transport of glucose in several tissues like that of kidney and small intestine. The reason for this was its inhibitory action on SGLT2and it was even able to induce glycosuria without posing the risk of hypoglycaemia. However, it could not be formulated into a drug due to

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its poor bioavailability and inhibitory action on Glucose Transporter. But all this gave us a novel approach to create SGLT2 inhibitors that have an insulin independent action. O-glucosidase derivatives of phlorizin were not formulated into drugs due to their poor selectivity towards SGLT2 and poor bioavailability. C-glucosidase derivatives of phlorizin include Dapagliflozin, Empagliflozin and Canagliflozin that have shown promising results in clinical trials and are now circulated in market as drugs for T2DM [42].

Drugs approved by FDA (Table 1)

Steglatro (Ertugliflozin) tablets and Segluromet (Ertugliflozin and metformin HCl): These oral hypoglycemic drugs were approved in December 2017 and were clinically tested by the company Merck and Co. [33].

Drugs under clinical trial (Table 1)

Remogliflozin Etabonate (RE) (100 mg, twice a daily tablet): It is a potent and selective inhibitor of SGLT-2 with a short half-life. After successfully completing its Phase one & two clinical trial, the drug showed effective reduction in HbA1c, fasting and post prandial glucose levels, systolic and diastolic pressure and weight loss in T2DM patients with uncontrolled hyperglycaemia in Phase 3 trial. RE is a prodrug that is de-esterified into Remogliflozin by non-specific esterases in the gastro-intestinal tract. Based on the results of Phase 3 clinical trials, RE(100 mg tablet) has been approved for adequate glycaemic control, together with diet and exercise in adults aged 18 years or above with T2DM by the Health Regulatory Authority of India [43].

- **Combination Drugs Targeting DPP-4 AND SGLT-2 Receptors:** These combination drugs have been developed to achieve effective glycaemic control accompanied by weight loss. This combination therapy is more effective in lowering blood glucose levels and HbA1c than DDP-4 or SGLT-2 inhibitors (DPP4i and sglt2i) alone. However, this combination is therapeutically effective only when SGLT2i are combined or added to DPP-4i, not vice-versa [44].

Drugs approved by FDA (Table 1)

a. Glyxambi: It was approved by FDA on 2nd February, 2015. It is a fixed dose combination of 10 or 25 mg empagliflozin combined with 5 mg Linagliptin in a tablet once daily to be given as an addition to exercise and diet in order to enhance glycaemic control type 2 diabetic patients [45].

b. Qtern Tablets: This is an oral hypoglycemic combination of dapagliflozin (acts on SGLT-2 protein) and saxagliptin (acts on DPP-4). The company that proposed this combination and conducted its clinical trial is Astra zeneca. FDA approved this drug in February 2017 [33].

c. Qternmet XR: It is a modified version of the Qtern tablet that is also made and tested by the same parent company i.e. Astra Zeneca. This oral combination drug is available in the form of an extended-release tablet and has metformin in addition to dapagliflozin and saxagliptin. It was approved by the FDA in December, 2019 [33].

- **Compounds and Receptors that are being put to clinical trials for testing their potency as Hypoglycaemic Drugs (Table 1):**

a. SIRTUIN-1 receptor as a novel target: SIRTUIN-1(SIRT-1) is a NAD+ dependent class 3 histone deacetylase. It regulates the glucose and lipid metabolism, reduces the oxidative stress in cells, positively regulates the secretion of insulin from β cells in pancreas and also aids in modulation of insulin signaling in metabolic pathways. However, high calorie intake, insulin resistance and high glucose tolerance in cells for a long period of time slows down the regulation of SIRT-1. Based on several trials performed in mice models, it has been found that Calorie Restriction (CR) without malnutrition could help in the activation of SIRT1, which can then regulate the glucose metabolism in patients with T2DM. However, the CR that we need requires a very strict diet for a very long time which is difficult for a person to follow. Thus, researchers are working on designing drugs that could target positive SIRT1 regulation in T2DM patients [46].

b. Obeticholic Acid as a novel therapeutic compound: Farsenoid X receptor is a nuclear hormone receptor involved in regulating the lipid and glucose metabolism. Obeticholic acid (OCA) is a semi-synthetic derivative of chenodeoxycholic acid and in a clinical trial; it has shown the ability to enhance the insulin sensitivity of cells and even reduced the indicators of insulin inflammation in patients suffering with non-alcoholic fatty liver disease and T2DM. In animal models, OCA has caused decrease in hepatic steatosis and insulin resistance [47].

c. G-Protein Coupled Receptor 40 (GPR40) as a novel target: GPR40 is expressed in β-cell of pancreas and even plays a role in stimulating Glucose Dependent Insulin Secretion (GDIS) in these cells when stimulated by extracellular Free Fatty Acids (FFAs). GPR40 is expressed in other tissues as well but to a lesser extent. Its role in GDIS has been supported by various pre-clinical studies in which its removal or reduced expression decreased insulin secretion from pancreatic β-cells and its overexpression improved GDIS in both wild-type and diabetic rats. Notably, antagonist GW1100 was able to inhibit the GPR40 induced GDIS from MNI6 cells in mice. It is also expressed in the entero endocrine cells and triggers the secretion of GLP-1 and GIP. As we have enough evidence from pre-clinical and clinical studies, GPR40 synthetic selective agonists- TAK-875 that mimic the structure of FFAs and a full agonist (stimulates the secretion of GLP-1 and GIP as well) - AM837 have been synthesized and these two are currently being tested in humans. These agonists successfully accentuate insulin secretion from pancreatic β-cells, help in restoring metabolic homeostasis and improve glucose tolerance. However, the β-cell oxidation caused by chronic exposure to synthetic FFAs and the receptor's role in insulin sensitivity is still being debated. However, as no study conducted has shown the risk of hypoglycemia, this novel target and its agonists seem a promising therapeutic tool for the treatment of T2DM [48].

Conclusion

With the above literature review, we further conclude that there is a far more potential for research in the advancements of numerous targets for the treatment of T2DM.

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