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Review Article

Management of Type 2 Diabetes Mellitus by DPP-IV Inhibition – A Review

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Abstract

Diabetes mellitus is one of the most prevalent chronic disorders worldwide. Type 2 diabetes mellitus (T2DM) involves multiple pathophysiological defects, accounting for nearly 85-95% of total reported cases of diabetes mellitus. Different classes of Oral Hypoglycemic Agents (OHA) are now available which target different pathophysiological factors leading to the management of T2DM; however, almost all of them are associated with one or the other kind of side effects. An alternative approach for the treatment of diabetes is based on targeting incretin hormone like Glucagon-like peptide-1(GLP-1). GLP-1 is an insulinotropic gut hormone which enhances meal induced, glucose-dependent insulin secretion (incretin effect) and restores glucose competency to the β -cells of pancreas including the delay of gastric emptying and suppression of appetite. However, the major limiting factor of GLP- 1 is its susceptibility to degradation by dipeptidyl peptidase IV (DPP-IV) enzyme. Also GLP-1 has a short plasma half-life of only 1-2 minutes. Inhibition of DPP-IV enhances the levels of endogenous active GLP-1 and prolongs its half-life, thereby becoming a requisite to identify DPP-IV inhibitors that can act as potential antidiabetic agents. In the wake of disadvantage due to the side effects caused by the synthetic drugs, natural sources of drugs like medicinal plants are in great demand all over the world. A large number of medicinal plants have been identified to have anti diabetic activity over the years. Few such plants have been identified to function as potential DPP IV inhibitors and are discussed in this review along with their synthetic counterparts.

1. INTRODUCTION

Diabetes is a clinical syndrome characterized by inappropriate hyperglycemia caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level[1]. It is the most common endocrine disorder, affecting as many as 200 million people worldwide, with the number estimated to grow up to 366 million or more by 2030 affecting both developed and developing countries alike. Type 2 diabetes is the world's fifth leading cause of death according to the World Health Organization[2]. India can be truly called the diabetes capital of the world with reference to the Diabetes Atlas 2009 published by the International Diabetes Federation which estimated diabetic population in India to be around 50.8 million, which is expected to rise to 87 million by 2030 [3].

All forms of diabetes have been managed since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Apart from insulin, few other drugs which can be administered orally are also used widely. Commonly known as Oral Hypoglycemic Drugs (OHD), they are classified in to different types according to their mode of action.Few major classes of oral hypoglycemic agents extensively used are: insulin secretagogues like sulfonylureas, Sensitizers like biguanides, thiazolidinediones and α glucosidase inhibitors. Each drug class works on different mechanism of action, which are briefly presented in Table 1. Insulin secretagogues or sulfonylureas increase the pancreatic insulin secretion by acting on the receptors present in islet cells of pancreas[4, 5].

Meglitinides also act as sulfonylureas, but the binding site is different [7,8]. They close the K^+ channels and open Ca^{2+} channels in the pancreatic beta cells and enhance the insulin production. Biguanides target hepatic insulin resistance, thereby reducing hepatic glucose output and increasing the uptake of glucose by the periphery, including skeletal muscles, enhancing the binding of insulin to its receptors and stimulating insulin mediated glucose disposal [11, 12].

Thiazolidinediones also known as "glitazones," bind to Peroxisome proliferator-activated receptor gamma (PPARγ), a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on Peroxysome Proliferator Responsive Elements (PPRE). The PPREs influence insulin sensitive genes, which enhance production of mRNAs of insulin dependent enzymes[14] whereas α glucosidase inhibitors delay intestinal carbohydrate absorption[15, 16].

2. DISADVANTAGES AND LIMITATIONS OF THE PRESENT HYPOGLYCEMIC DRUGS

Over the years, several studies have been conducted to find out the adverse side effects posed by certain diabetes drugs. Among these side effects, cardiovascular risks, hypoglycaemia and weight gain are major concerns (Briefly represented in Table 1).

Sulfonylureas are known to increase the risk of congestive heart failures by 18 to 30% [18] in the patients treated with them and are also associated with hypoglycemia[6] and weight gain [19,20]. Meglitinides are also associated with hypoglycemia[9] and respiratory infection[10]. Thiazolidinediones like Rosiglitazone was found to be associated with higher risk of cardiovascular event and significant increase in risk of myocardial infraction[15] along with pioglitazone[21]. Metformin, which is a biguanide, is being consistently associated with high incidence of diarrhoea as a common side effect[13]. α - Glucosidase inhibitors are often associated with abdominal bloating and discomfort along with flatulence[17].

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Table 1: Targets for diabetes and their side effects

Drug group	Members of the group	Targets	References	Side effects	References
Sulfonylureas	Glibenclamide, Glyclopyramide, Glimepride	Stimulating insulin release by pancreatic beta cells	[4,5]	Hypoglycemia , minor skin allergy	[6]
Meglitinides	Repaglinide, Nateglinide, Mitiglinide	Stimulate the pancreas to release insulin	[7,8]	Hypoglycemia, gastro-intestinal upset	[9,10]
Biguanides	Metformin, Buformin, Phenformin	Reduce hepatic glucose output and increase the peripheral uptake of glucose	[11,12]	Lactic acidosis, nausea, diarrhea and gastro-intestinal upset	[13]
Thiazolidinediones	Rosiglitazone, Pioglitazone, Troglitazone	Bind to PPARγ	[14]	Fluid retention, edema or weight gain, increased risk of myocardial infracion	[15]
α-glucosidase inhibitors	Acarbose, Miglitol, Voglibose	Delay intestinal carbohydrate absorption	[16]	Flatulence, abdominal discomfort	[17]

3. TARGETING GLP-1 AS AN ALTERNATE APPROACH IN TREATMENT OF DIABETES

An alternative approach for treatment of type 2 diabetes mellitus is based on targeting incretin hormone (GLP-1), which has helped in better understanding of their potential, which in turn has led to the development of incretin analogs and incretin enhancers for treatment of type 2 diabetes mellitus.

4. MECHANISM OF ACTION OF GLP-1 AND DPP-IV

Glucagon-like peptide-1 (GLP-1) is an insulinotropic gut hormone. Secretion of GLP-1 occurs from the enteroendocrine L cells of distil small intestine[22]. It enhances meal induced, glucose-dependent insulin secretion (incretin effect) and restores glucose competency to the β-cells of pancreas[23,24]. GLP-1 also inhibits meal-induced gastric acid secretion, gastric emptying, and thereby reducing postprandial glucose excursions which is an advantage in type2 diabetes[25]. Circulating levels of GLP-1 are low in the fasting individuals and the level of it rises quickly after meals. However, the major limiting factor of GLP- 1 is its susceptibility to degradation by dipeptidyl peptidase IV (DPP-IV) enzyme resulting in a half-life of active GLP-1 of only approximately 1-2 minutes. Inhibition of DPP-IV automatically increases the levels of endogenous active GLP-1 and prolongs its half-life.The mechanism of action is represented in Fig.1.

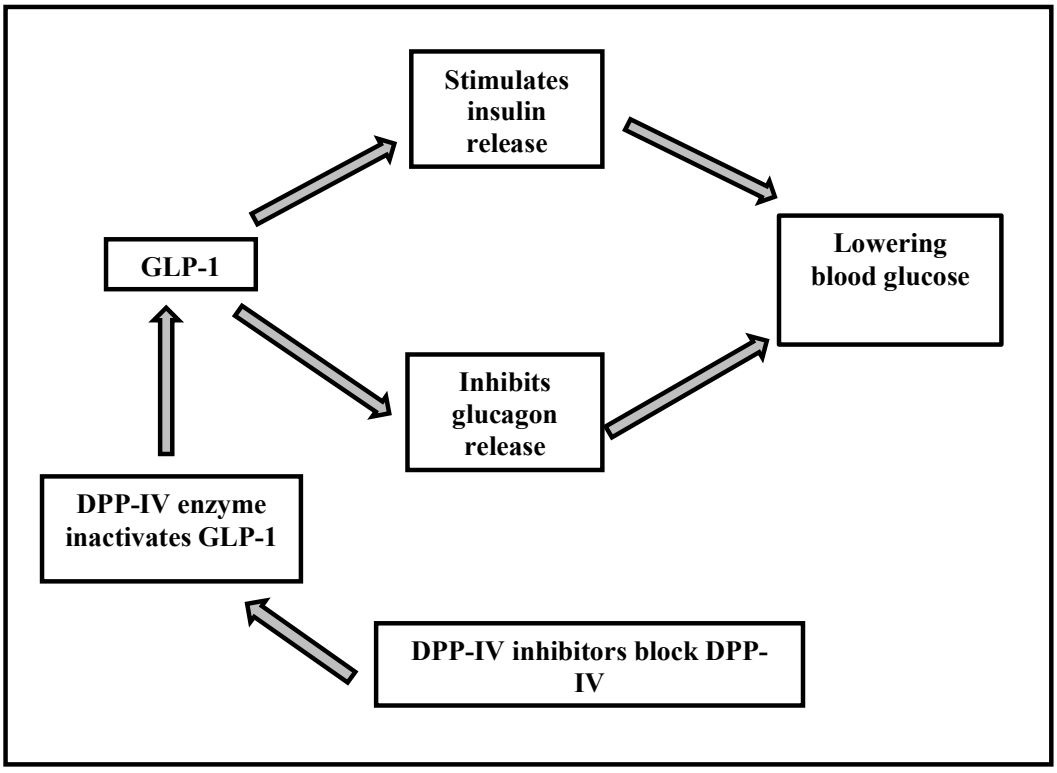


Fig 1: Mechanism of action of GLP-1 and DPP-IV

DPP-IV also known as CD26, was described for the first time by Hopsu-Havu and Glenner in 1966[26]. DPP-IV is widely distributed in tissues, such as lung, spleen, liver, kidney, intestines, endothelial cells, bone marrow and blood cells, and is also present in serum in the form of soluble protein[27, 28]. It is a serine protease found on the surface of varieties of cells with a catalytic activity which removes

the N terminal dipeptides with proline or alanine at the penultimate position of various peptide substrates including inflammatory cytokines and chemokines[29, 30, 31]. The proteolytic action of DPP-IV is one of the multiple functions of the protein along with other functions such as receptor activity, co-stimulatory functions, binding and interactions with various proteins, and also play a role in apoptosis[31].

Another class of drugs which has come to use in recent years for the treatment of diabetes are GLP-1 analogues and agonists about which is given below.

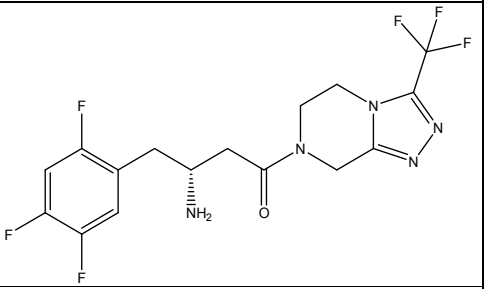
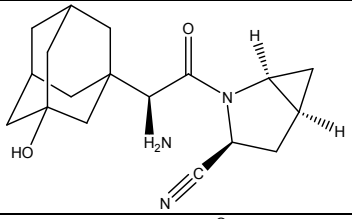
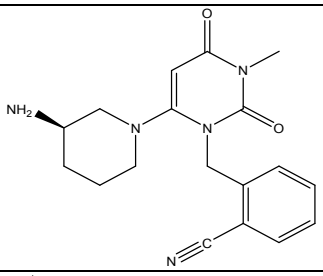
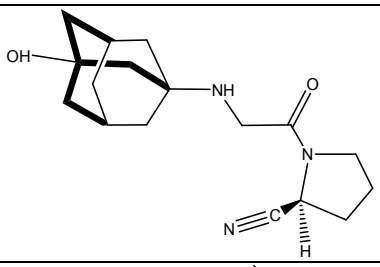
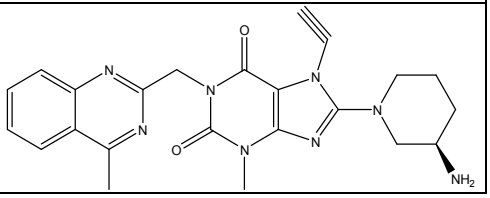
5. GLUCAGON-LIKE PEPTIDE ANALOGUES AND AGONISTS

Long term acting analogues of GLP-1, which maintain the effects of GLP-1and resistant to the action of DPP-IV are also called incretin mimetics. Exenatide is a GLP agonist which enhances glucose-dependent stimulation of insulin secretion, suppresses the inappropriate glucagon secretion and slows down the gastric emptying, and help enhance beta cell mass [32, 33]. Liraglutide is a human GLP-1 analogue[34] which has 97% homology, has been developed recently and approved by FDA in 2010.

6. ROLE OF DPP IV INHIBITORS IN THE TREATMENT OF TYPE 2 DIABETES

DPP-IV inhibitors have a major advantage over other diabetes medications wherein glucose control remains stable with little or no rise in HbA1c levels for long periods of use along with favorable adverse-effect profile, and a neutral side effect on weight[35]. DPP-IV also stimulates a number of regulatory functions, including the hydrolysis of several peptide hormones and chemokines and a co-stimulatory effect of T-cell activation via its signaling function[36].

Table 2: Structures of few synthetic DPP-IV inhibitors

Name	Chemical Name (IUPAC)	Structure
Sitagliptin	(*R*)-4-oxo-4-[3-(trifluoromethly)-5,6-dihydro[1,2,4]triazolo[4,3-α] pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenly) butan-2-amine	
Saxagliptin	(1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile	
Alogliptin	2({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile	
Vildagliptin	(S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile	
Linagliptin	8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3- methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione	

Treating diabetic rodents with DPP-IV inhibitors has proven to improve islet survival and maintains beta cell mass and islet function[37]. Oral administration of Ile-thiazolidide (a specific DPP IV inhibitor), has been known to show rapid inhibition of circulating DPP-IV levels and improved glucose tolarence in obese and lean Zucker rats[38]. Preclinical studies have demonstrated that DPP-IV

inhibition could prevent the degradation of GLP-1 *in vivo*, leading to increased insulinotropic activity[39], followed by the first demonstration in humans, that a DPP-IV inhibitor could improve glycaemic control in subjects with T2DM[40]. Therefore, it becomes a requisite to identify DPP-IV inhibitors that can act as potential antidiabetic agents.

The principle of using DPP-IV inhibitors as therapy of T2DM [25, 41] is now firmly established and numerous synthetic inhibitors are in varying stages of clinical development among which the four already approved are sitagliptin in 2006, vildagliptin in 2007, saxagliptin in 2009, alogliptin in 2010 and the fifth one, linagliptin (currently in phase 3 clinical development). These synthetic DPP-IV inhibitors along with their IUPAC names and structures are presented in Table 2.

The present synthetic DPP-IV inhibitors contain various groups of compounds which are mainly divided into two types, those that have similar dipeptide structure as that of DPP-IV substrates and the ones that are non-peptidomimetic. The nitrile containing DPP-IV inhibitors such as sitagliptin[42, 43], vildagliptin[44,45] and saxagliptin[46] have the structures similar to that of DPP-IV substrates. Whereas the inhibitors that are non-peptidomimetic are alogliptin[47,48] and linagliptin[49,50].

On the other hand, there are naturally occurring active components which can be derived from plant sources. Over centuries plants were the first preferred sources of medicine, the knowledge which has been passed down from generation to generation in different cultures including Indian, Egyptian, Native American, European and Chinese. A number of medicinal plants, traditionally used for thousands of years are present in herbal preparations of Indian traditional health care systems [51]. In the last few years there has been significant interest in the field of herbal medicine due to their popularity both in developing and developed countries because of their natural origin and minimal side effects. Furthermore, with the help of developing scientific technology, it is now much easier to identify the active components, their mode of action which is widely utilized to develop natural drugs thus providing a new understanding into pharmacological aspects.

7. DPP IV INHIBITION USING PLANT SOURCE

Mangifera indica L. is a popular tropical fruit and most parts of the tree like the fruit, seeds, pulp, stem bark, roots and leaves have many medicinal properties [52]. A study on *Mangifera indica* leaves was carried out by Yogisha *et al*., in 2010[53]. In the above mentioned study, the methanolic extract of *Mangifera indica* leaves was tested in DPP - IV inhibitory activity. The assay was carried out according to Kojima *et al.,* (1980)[54] using a chromogenic substrate Gly-pro-pnitroanilide and Diprotein-A as reference inhibitor. Diprotein - A is a tripeptide (Ile-Pro-Ile) and an effective DPP-IV inhibitor [55]. Porcine kidney DPP-IV was inhibited with an IC50 value of 182.7µg/ml by the methanolic extract of *Mangifera indica* leaves.

Similar studies were carried out by Chakrabarti *et al*., in 2011[56]. The plants screened for DPP-IV inhibition by *in vitro* assay are as follows : *Berberis aristata* (bark), *Pongamia pinnata* (seed), *Cassia auriculata* (flower), *Szygium cumini* (seed), *Terminalia chebula* (fruit), *Terminalia arjuna* (bark), *Salvadora persica* (bark) and *Punica granatum* (seed). The assay method of Al-masri, *et al*., (2009)[57] was modified and standardized using Diprotein A as the standard DPP-IV inhibitor. Different concentrations of methanolic plant extracts were tested for DPP-IV inhibitory activity. *Szygium cumini* showed the highest inhibition of 87% which is followed by *Berberis aristata* with 73% and *Terminalia chebula* with 51%. Berberine (structure represented in Fig.2), which is a quaternary ammonium salt, is present in *Berberis aristata,* due to whose presence, the plant was selected for further studies.

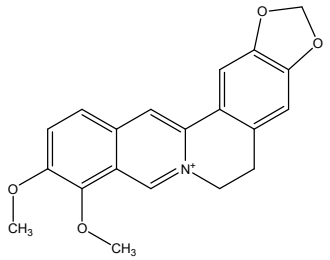


Fig 2: Structure of Berberine

The bark extract of this plant showed IC50 value of 14.46 µg/ml and that of Diprotein-A was 1.543µg/ml.

DPP- IV inhibition was also studied in some of the Armenian plants[58]**.** In the study, the inhibitory ability of aqueous extracts of 28 plants of different origin, traditionally used in folk medicine and/or as food in Armenia were tested for their DPP-IV inhibitory activity. The IC50 values for inhibition of DPP-IV by the selected plant extracts is as follows; *Hippophae rhamnoides*- 2.56 mg/ml, *Rubus caesius* - 6.76 mg/ml, *Helichrysum rubicundum* - 9.46 mg/ml, *Origanum vulgare* - 11.86 mg/ml and *Mentha piperita*-13.6 mg/ml.

The DPP-IV inhibitory potential of *Castanospermum austral* Cunn., seed extract was reported by Bharati *et al*., (2012)[59]. The IC50 value of the exract and Diprotein – A was reported to be 13.96 µg/ml and 1.543 µg/ml respectively. Further, the molecular docking of three alkaloids present in the seeds of *C. australe* showed DPP-IV inhibition which was comparable to berberine. The study has also reported that the alkaloid 7-Deoxy-6-epi-castanospermine is a potent DPP-IV inhibitor alike berberine. In diabetic rats, treatment with the *C. australe* extract reduced the elevated levels of blood glucose and HbA1c with significant improvement in Oral Glucose Tolerance [59].

A very recent study on DPP-IV inhibitory activity of *Amaranthus hypochondriacus* was reported by Velarde *et al*., in 2013[60]. Amaranthus seeds were reported to have DPP-IV inhibitory peptides which were identified with the help of LC/MS-MS [61]. A comparative study was carried out for the peptides derived from soybean, black bean and wheat. The molecular mechanism of interaction between seed peptides with DPP-IV was established with the help of docking modelling. Glutin hydrolysates present in Amaranthus showed inhibition against DPP-IV which decreased dose dependently showing the IC50 value ranging from 1.2 to 2.0 mg/mL with respect to enzyme to substrate ratio. Raw amaranthus flour showed highest inhibitory activity of upto 50 % with an IC 50 value of 1.1 mg/mL followed by wheat flour with IC50 value of 0.8 mg/mL and soybean flour with 1.4 mg/mL [60].

8. CONCLUSION

The national medicinal plants board of India has estimated that more than six thousand plants in India are used for their medicinal properties in different systems of medicine, like ayurveda, homeopathy, unani etc. A number of primary and secondary metabolites synthesized by plants help perform important biological functions and have known to show long term health benefits when consumed in proper dosage. Medicinal plants also play an important role in the treatment of various ailments and diseases in developing countries where the resources are minimal. In this context, further work regarding the identification and screening of other herbal medicinal plants, which are abundantly available in our surroundings, must be carried out in the future for their DPP-IV inhibitory activity. Keeping in mind the side effects associated with the existing synthetic drugs, the natural origin of plant bioactives are expected to gain popularity. In addition, these bioactives are expected to be economically efficient, easily accessible and readily acceptable by the people around the world.

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