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Recent Advancement In DPP-4 Inhibitors For The Treatment of T2DM

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Abstract

Diabetes is a heterogeneous metabolic disorder having common features of chronic hyperglycaemia causing imbalance in carbohydrate, fat and protein metabolisms. Irregular insulin secretions or action or both can lead to hyperglycaemia in diabetes. Today, diabetes mellitus has become the most common cause of mortality and morbidity worldwide. Approximately, 80 % of the total diabetes burden is carried by the low and middle-income countries. It has affected more than 425 million people at present, and it was estimated that this number may increase up to 693 million by 2045. Several classes of anti-hyperglycaemic agents are used as mono or combination therapy to treat diabetes mellitus. These include meglitinides, biguanides, sulphonyl ureas, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors and incretin mimetics.

Keywords: Diabetes, Hyperglycaemia, Antidiabetic agents, DPP-IV inhibitors.

INTRODUCTION

Diabetes is a heterogeneous metabolic disorder having common features of chronic hyperglycaemia causing imbalance in carbohydrate, fat and protein metabolisms [1]. It has occupied its position in the list of most common causes of morbidity and mortality worldwide. Sedentary lifestyles, rapid urbanization and unhealthy diets lead to the higher rates of diabetes and obesity.[2] At present more than 425 million people are affected by diabetes, out of which 1/3rd are the people having age more than 65 years. Recently, it was estimated that this number may increase up to 693 million by 2045. Increment in North American and Caribbean diabetic patients would be up to 35%, in North Africa and middle east increment would be 72%, Europe would face increment up to 16%, increment in south and central American patients may go to 62%, in South-East Asia increment would be 84%, the least increment i.e. 15% would be in patients of West Pacific whereas the highest increment in diabetic patients would be faced by Africa i.e. 156% by 2045.

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Over than a million people having age less than 19 are affected by type-1 diabetes mellitus. Approximately, 80 % of the total diabetes burden is carried by the low and middle income countries. People suffering from impaired glucose tolerance (more than 352 million) are at higher risk of developing diabetes. The data may get doubled by 2045 in many regions.[3]

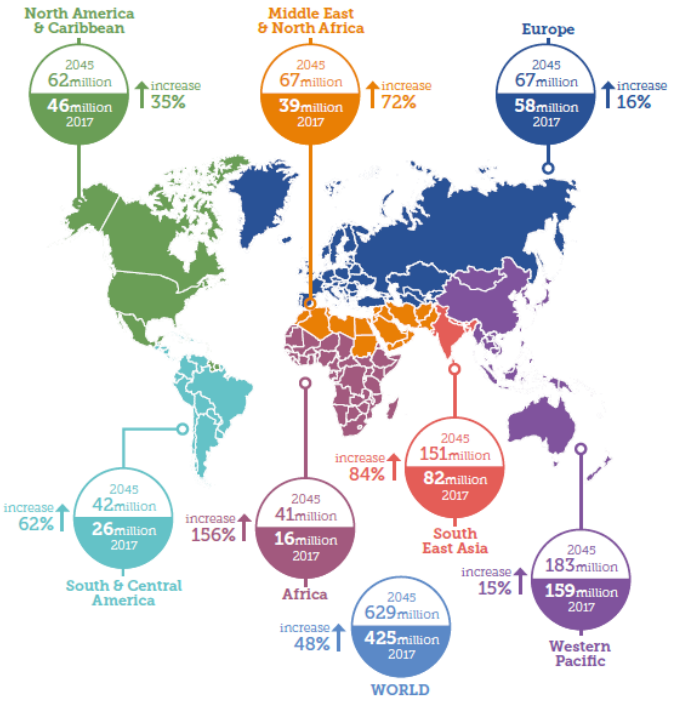

Fig. 1: worldwide diabetes prevalence data and the probability of increment in diabetic patients by 2045 according to current conditions. (3)

In 2017, the data collected by IDF regarding the worldwide expenditure over the treatment of diabetes illustrates the top 10 countries which have spent the maximum amount of money including both public and private healthcare expenditures. (Table 1) [3]

Table 1: Country-wise total healthcare expenditure over the treatment of diabetes.

Rank	Countries	Total healthcare expenditure (Billion ID)
1	United States of America	348
2	China	110
3	India	42
4	Germany	31
5	Japan	28
6	Brazil	24
7	Russian Federation	20
8	Mexico	19
9	France	18
10	Canada	15

ID: A hypothetical unit of currency which possess the similar purchasing power in every country (Dollars can be used to compare expenditures among different countries or regions).

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To get control over this widely spreading disease WHO (World Health Organisation) has given some recommendations for the extent of physical activity one should perform daily to remain healthy. (Table 2) [4]

Table 2: Recommendations by WHO for the extent of physical activity.

Age (years)	Physical activity	Time (minutes)
5 to 17	Moderate*	60
18 to 64	Moderate* Vigorous#	150 75
> 64	Same amount of physical activity is recommended, but also include balance and muscle strengthening activity tailored to their ability and circumstances	60

*Moderate physical activity refers to brisk walking, jogging, gardening etc. on weekly basis

#Vigorous physical activity refers to aerobic physical activity.

Major types of diabetes mellitus i.e. Type 2 diabetes mellitus (T2DM) and Type 1 diabetes mellitus (T1DM). Deficiency of insulin in blood circulation and destruction of pancreatic β-cells are the characteristics of auto-immune disease T1DM, whereas insulin resistance is the characteristic feature of T2DM in which target tissues fail to respond normally to insulin.[1] Glucose uptake is reduced by the muscle cells in Insulin resistance, and therefore oxidation of fatty acids and glycolysis in liver also decreases. It is then followed by decrease in the suppression of hepatic gluconeogenesis and the blood sugar level gets increased.

The potent inhibitors of insulin signaling are metabolic products of fatty acids and intracellular triglycerides. The insulin signaling is also decreased directly via FFAs (Free Fatty Acids) in excess and indirectly by the release of cytokines.[2] Due to dysfunction of β-cells, the insulin secretion is inadequate and these cells are unable to fulfill the long-term need of increased insulin secretion and peripheral insulin resistance. Initially, the level of insulin secretion is higher for every increase in glucose level during insulin resistance and this process maintains the normal plasma glucose levels for years by acting as a compensation for peripheral resistance, but later this compensation fails resulting in complete loss of β-cell mass and hence leads to hyperglycemia.[2] Therefore, inadequate insulin secretion and insulin resistance are the causes for T2DM [5, 6]. Other than these environmental factors like sedentary lifestyle, dietary habits etc. may also lead to diabetes mellitus.

The T2DM has now emerged into a disorder that is affecting younger population distressed with abnormal adipocyte function and central obesity. [7, 8] People having T2DM and obesity are leptin as well as insulin resistant, that modifies the normal fuel feedback to the brain and the CNS becomes the critical player in dysregulation of glucose.[7] [9]

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If the hyperglycemia remains unchecked for a long period of time various health complications like cardiovascular disease, nephropathy, neuropathy, retinopathy, blindness occurs. Early diagnosis of diabetes can prevent such complications.[2]

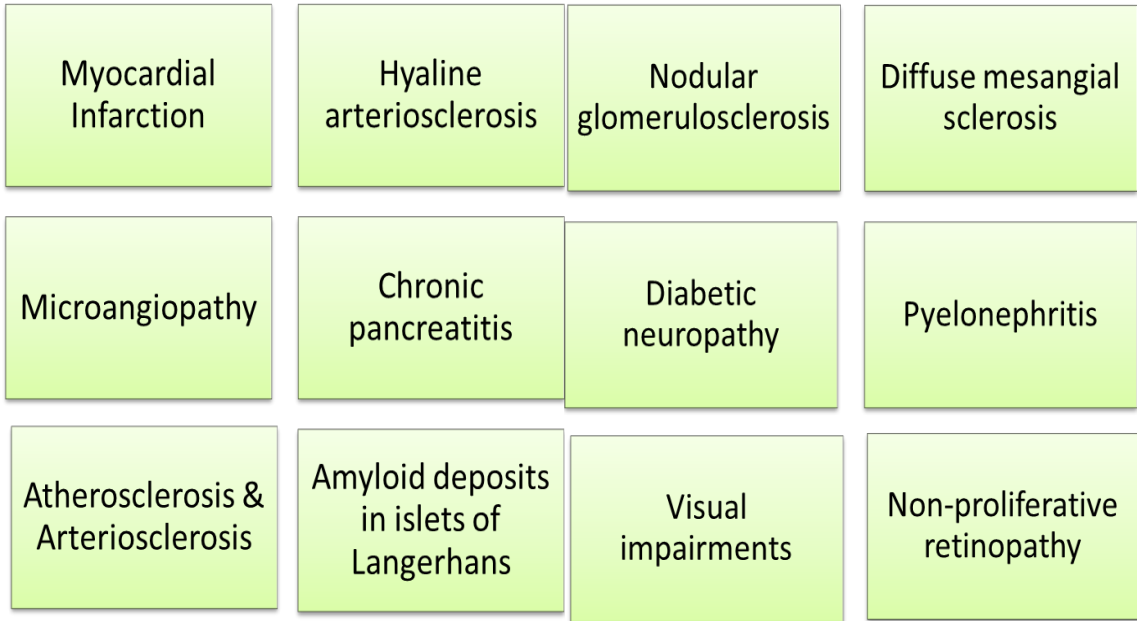

Fig. 2: Various health complications that could arise due to type-2 diabetes mellitus.

World Health Organization has provided the criteria to diagnose diabetes that considers hyperglycaemia as the major characteristic to diagnose diabetes (Table 3). The blood glucose level in a normal person remains below 100 mg/dl but in the diabetic patients it may go above 200 mg/dl.[3] Clinically the glycaemic control is determined by the percentage amount of HbA_{1C} in blood also called as glycosylated hemoglobin formed by non-enzymatic addition of glucose to hemoglobin in RBCs. The HbA_{1C} level in normal people is between 4% to 5.6% and in diabetic people it may be equal to or more than 6.5% .[10].

Table 3: The diagnostic criteria provided by the World Health Organization (WHO) for the diagnosis of T2DM.[3]

Positive test for diabetes if one or more of the following criteria's are fulfilled	If FPG is more than or equals to 7 millimol per litre or 126 milligram per decilitre **Or** 2 Hours plasma glucose is more than or equals to 11.1 millimol per litre or 200 milligram per decilitre after a oral glucose load of 75 grams **Or** A random glucose is more than 11.1 millimol per litre or 200 milligrams per decilitre or if HbA1c is more than or equals to 48 millimol per mol which is equivalent to 6.5 percent

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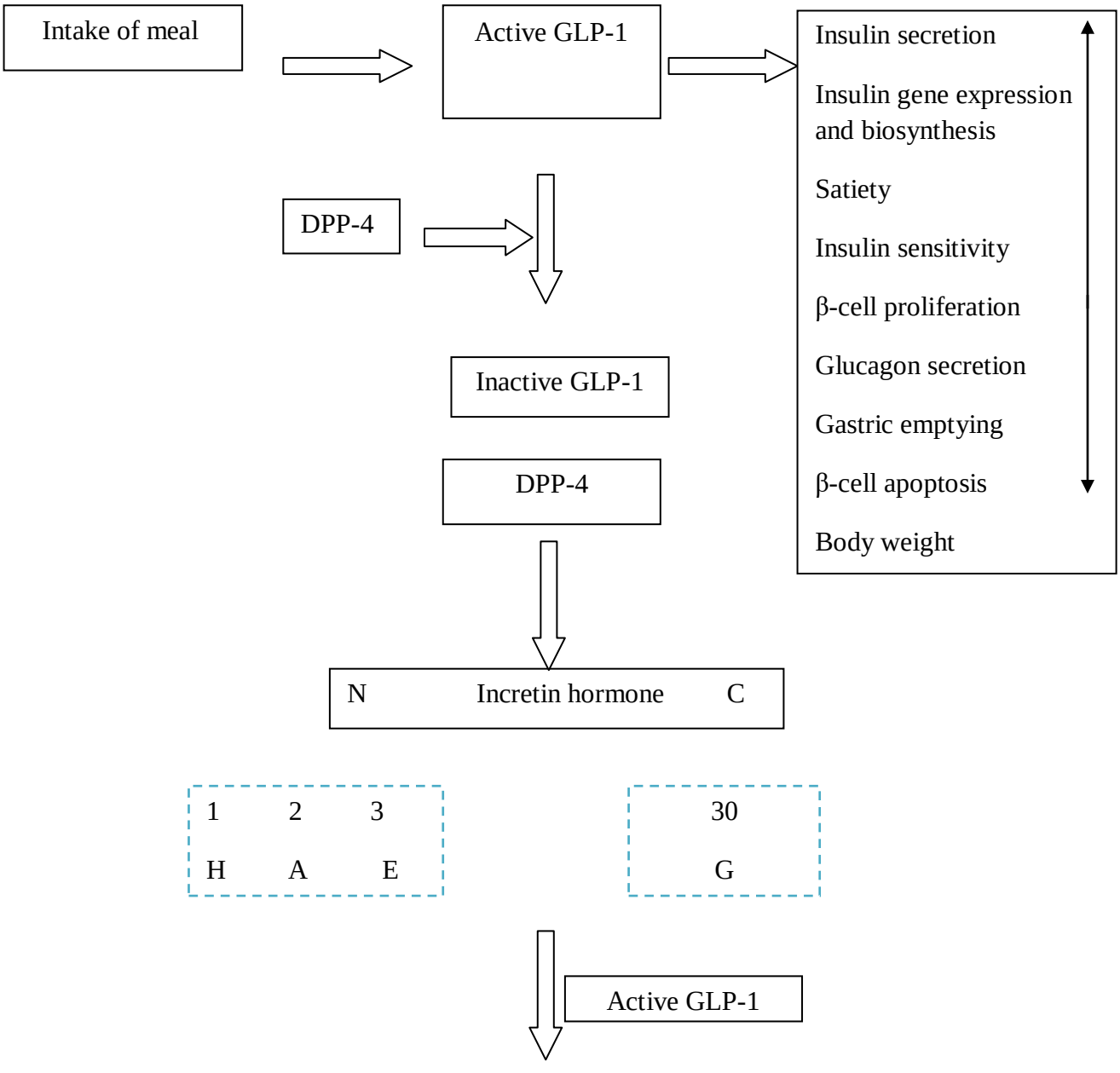
Positive test for impaired glucose tolerance (IGT) if both of the following criteria's are fulfilled	If FPG is more than 7 millimol per litre or 126 milligrams per decilitre **and** If 2 hours plasma glucose is more than or equals to 7.8 but less than 11.1 millimol per litre or more than or equals to 140 but less than 200 milligrams per decilitre after an oral glucose load of 75 grams.
Positive test for impaired fasting glucose (IFG) if any of the following criteria's are fulfilled	If FPG is 6.1 to 6.9 millimol per litre or 110 to 125 milligrams per decilitre **Or** If 2 hours plasma glucose is less than 7.8 millimol per litre or 140 milligrams per decilitre after an oral glucose load of 75 grams.



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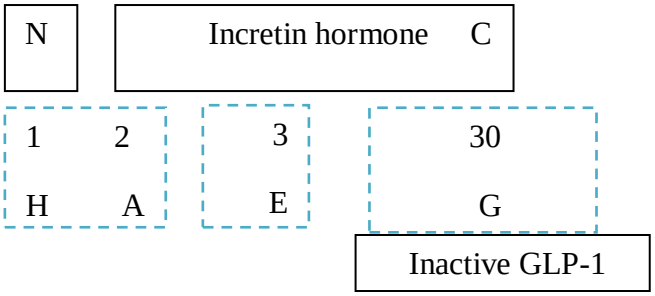

Fig.3: DPP-4 cleaves the incretin hormones GLP-1 and glucose dependent insulin tropic polypeptide (GIP) in their second position where alanine is present.

The recommended first line treatment in case of diabetes mellitus is metformin when the desired glycemic goals are not achieved by non-pharmacological approaches like changes in lifestyle, exercise, diet etc.[11]

Metformin inhibits gluconeogenesis, hence reduces HbA_{1c} levels which leads to decreased hepatic glucose production. One of the following drugs can be added to metformin therapy including glucagon-like peptide-1 receptor (GLP-1R) agonist, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, thiazolidinedione, sulfonylurea, DPP-4 inhibitor etc.[12] If even after 3 months of the metformin therapy the HbA_{1c} target isn't achieved then basal insulin can also be used in metformin monotherapy. Even if HbA_{1c} targets remain unmet after dual, metformin-based treatment, diabetic patients may advance to triple therapy or to more complex injectable therapies, including the side effects of nausea, hypoglycaemia, vomiting etc.[2, 4, 6]

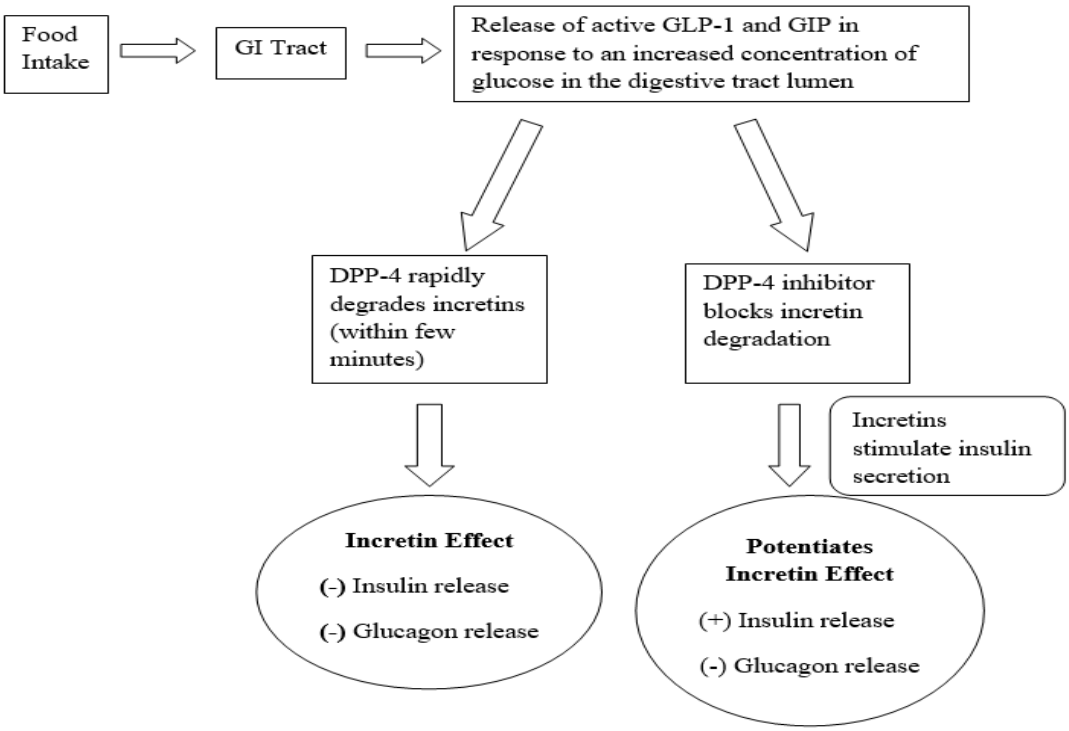

Fig. 4: Effects of actions of DPP-4 enzyme and DPP-4 inhibitors in diabetic patients.

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GLP-1 is one of the novel approaches to treat T2DM and it is secreted into two major forms GLP-1(7, 37) and GLP-1(7, 36). In response to nutrients these forms are secreted from the glucagon gene in L and K cells present in the small intestine. GLP-1 helps in increasing the growth of β-cell mass and it is responsible for the inhibition of cell apoptosis that occurs during type-2 DM in the β-cells of pancreas. The antidiabetic action of GLP-1 is reported as it stimulates the secretion of insulin, inhibits the secretion of glucagon, reduces the gastric emptying rate and increases satiety.[13-17]

The function and potential role of GLP-1 was first reported in the late 1990s.[15, 17] The inhibition of DPP-4 enzyme is the mechanism of action of GLP-1 based therapies. DPP-4 inhibitors are weight neutral, have shown improved functions of β-cells in animals including in-vitro studies and don't cause hypoglycaemia until they are combined with the drugs that cause hypoglycaemia.[18, 19] The inhibition of DPP-4 have shown improvement in the glycemic control with 0.6 to 1.1% reductions in HbA1c levels during clinical trials.[20] DPP-4 enzyme also called as cluster of differentiation-26 (CD26).[21, 22] DPP-4 enzyme plays vital role in the metabolism of glucose.[22]

Many bioactive peptides like GLP-1 and GIP are deactivated by the DPP-4 enzyme which is expressed on various types of cells in the body. Due to this, the half-life of these bioactive peptides is 1-2 mins in the blood circulation. DPP-4 enzyme cleaves the amino acid chain at the 2^{nd} position of GLP-1 (alanine) and thereby degrades it.[23, 24] This results in conversion of active GLP-1(7, 37) and GLP-1(7, 36) to inactive GLP-1(9, 37) and GLP-1(9, 36). DPP-4 inhibitor blocks the activity on GLP-1 and GIP in systemic circulation and regulates glucose levels in blood through multiple effects that are already mentioned above.[13, 25, 26]

The pyrrolidine containing peptidomimetic based DPP-IV inhibitors were designed, synthesised and biologically evaluated by Jadav P.et al.[27]

After observing the results of in-vitro studies, both the compounds, Compound-1 and Compound-2 were found to be selective as well as potent. Male C57BL/6J mice were evaluated for in-vivo study using IPGTT. The observed changes in serum glucose levels (AUC_{240min}; mg/dl) were reported. Average activity i.e. percent decrease in glucose AUC (17.4 ± 5.35 and 21.5 ± 6.1) was shown by NVP-DPP728 and Compound-2 respectively with blood glucose level suppression at 30 minutes and 60 minutes, whereas Compound-1 possessed better oral antidiabetic activity (percent decrease in glucose AUC by 54.9 ± 3.89) with blood glucose suppression level at all the time points i.e. 30, 60, 120 and 240 min.

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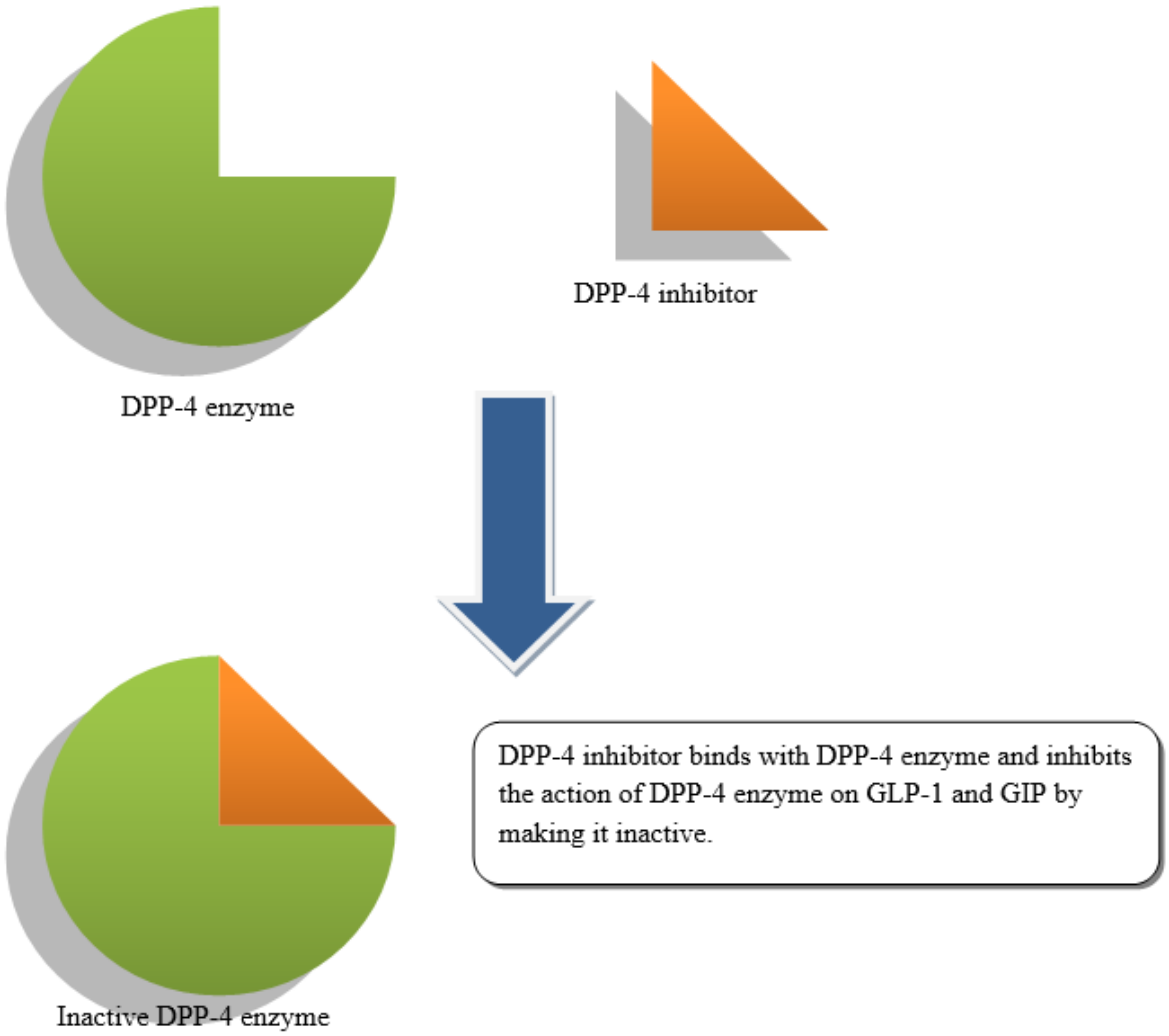

Fig. 5: Inhibition process of DPP-4 enzyme by DPP-4 inhibitors.

Various pharmacokinetic parameters were recorded including $T_{½}$, AUC, T_{max}, C_{max} and %F. A rapid T_{max}, good C_{max} and oral bioavailability (%F= 63-72%) were shown by all the test compounds. As compared to NVP-DPP 728 and Compound-2, Compound-1 showed extended half-life ($T_{1/2}$ more than 7 h) that might be due to its low clearance, for Compound-1 it was 0.11 ± 0.03 and for Compound-2 it was 0.82 ± 0.18 and better AUC (more than two folds). In fed animals (those are hyperglycaemic), similar results were obtained. In-vitro inhibitory activity of DPP-IV inhibitors (3 folds potent) over NVP-DPP728 was justified after carrying out in-silico study to observe the Compound-1 additional interactions in third state of DPP-4 enzyme.[27] The compounds taken for study are shown in Fig 6 and the observation values for all three compounds are shown in table 4.

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Compound 1 Compound 2 NVP-DPP-728

Fig. 6: Peptidomimetic based DPP-IV inhibitors containing pyrrolidine ring.

Table 4: Various pharmacokinetic parameters of peptidomimetic based DPP-IV inhibitors containing pyrrolidine ring.

Compound	T_{max} (h)	C_{max} (µg/ml)	$T_{1/2}$ (h)	AUC (µg/ml)	F^{*} (%)
Compound-1	0.29 ± 0.11	7.1 ± 0.83	7.99 ± 0.33	14.3 ± 1.13	72.5
Compound-2	0.28 ± 0.10	5.9 ± 0.88	0.99 ± 0.14	6.89 ± 1.21	63.1
NVPDPP-728	0.32 ± 0.08	6.2 ± 0.91	0.88 ± 0.11	6.49 ± 1.11	65

In another study by Bouchentouf S. et al interactions among the DPP-4 enzyme and the main constituents of cinnamon were studied using molecular modelling methods.[28] Usually, the medicinal effects are provided by the cinnamon bark, but here it was observed that as compared to the bark, the chemical constituents of buds and flowers of cinnamon were involved in the inhibition of DPP-4 enzyme [Table 5].[28]

Table 5: Various constituents present in different parts of cinnamon.

Part of the Plant	Compounds
C. zeylanicum bark	Cinnamaldehyde:65.00 to 80.00% Eugenol:5.00 to 10.00%
C. zeylanicum buds	Terpene hydrocarbons:78.00% *alpha*-Bergamotene:27.38% *alpha*-Copaene:23.05% Oxygenated terpenoids:9.00%
C. zeylanicum flowers	(E)-Cinnamyl acetate:41.98% *trans-alpha*-Bergamotene:7.97% Caryophyllene oxide:7.20%

In a search for natural DPP-4 inhibitors, Kim B.R. et. al found by performing in-vitro studies with human recombinant DPP-4 that three flavonol glycosides (compounds a, b and, c) which were isolated from seeds of Lens culinaris Medikus possess concentration dependent DPP-4 inhibitory activity. [29]. It has already been known that for recognising the ligands as DPP-4 inhibitors, pockets

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S1 and S2 are of great importance, and it was seen that all the three glycosides had optimum interactions with S1 and S2 pockets. [30]

Compound a

Compound b

Compound c

Fig 7: Flavanol glycosides islotaed from seeds of Lens culinaris Medikus.

Riyanti P. et al studied DPP-4 inhibiton of few Indonesian plants and found that out of 20 extracts, 5 different extracts of pomegranates rind of P. granatum L, bungur leaves of L. loudonii Teijsm. &

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Binn, brotowali stem of T. crispa Miers ex Hoff.f, bodhi leaves F. religiosa L., and fenugreek seeds of T. foenum-graecum L. had in-vitro DPP-4 inhibitory activity taking sitagliptin as a standard. Even out of these 5 extracts, the 5th extract i.e. extract of fenugreek seeds had highest DPP-4 inhibitory activity followed by the extracts of bodhi leaves, brotowali stem, bungur leaves, and pomegranate rind respectively.[31]

As compared to the other available antidiabetic drugs, the major advantages of DPP-4 inhibitors include; the improvements in β-cell's function, are weight neutral and have less risk for hypoglycaemia because of strict glucose-dependence of glucagonostatic and insulinotropic actions. Till date, the US-FDA has approved only four DPP-4 inhibitors [Table 6] including saxagliptin, sitagliptin, alogliptin and linagliptin.(31)

Table 6: Approved DPP-4 inhibitor drugs along with their year of approval.

Drug Name	Structure	Year of approval
Saxagliptin		2008
Linagliptin		2011
Sitagliptin		2012

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Alogliptin		2015
Tenegliptin		2012
Trelagliptin		2015
Evogliptin		2015
Omarigliptin		2015

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Anagliptin		2012
Vildagliptin		2007

Patients should be treated as a whole instead of just hyperglycaemia. For instance, patients diagnosed with T2DM are having high risk of cardio-vascular (CV) diseases, and they should be treated for the different risk factors of CV disorders including hypertension, obesity and dyslipidaemia as well.[7, 32] Patients diagnosed with T2DM along with chronic kidney disease are at higher risk of hypoglycaemia.[33] Therefore, treatment should be done considering all the above factors as well.

In cardiovascular physiology and atherosclerosis, the role of DPP-4 enzyme was discussed by Zhong J. et al. They highlighted that there is alteration of the pathways responsible for cardio-protection due to the inhibition of DPP-4 enzymes by DPP-4 inhibitors. From the results of clinical trials it was concluded that for short term as well as for long term (less than five years) DPP-4 inhibitors are safe for use. As compared to sitagliptin and alogliptin, it was observed that the heart failure rate was increased by saxagliptin.[34]

DPP-4 inhibitors have shown side effects like hypoglycaemia and pancreatic inflammation when prescribed along with other medicines taken for treating allergic reactions and diabetes together.[35] Hence, there is still a requirement of better new agents to treat T2DM. [12, 36, 37]

CONCLUSION:

Diabetes (increased blood glucose levels) has become one of the major causes of morbidity and mortality globally. Currently various drugs are available in the market for the treatment of diabetes. Targeting the TYPE-2 Diabetes, first line choice drug i.e. metformin is preferred over all others. Other than this, DPP-4 inhibitors have evolved as a better option for treating diabetes including drugs such as linagliptin, sitagliptin, saxagliptin, etc. Owing to the side effects of various drugs under DPP-4 inhibitors a better agent is required for treating TYPE-2 diabetes.

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