A Review of Dipeptidyl Peptidase-4 (DPP-4) and its potential synthetic derivatives in the management of Diabetes Mellitus

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Abstract

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a type of oral medication used to treat type 2 diabetes mellitus (T2DM). They have become increasingly popular due to their effectiveness and safety in managing the condition. DPP-4 inhibitors function by inhibiting the enzyme that breaks down the incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These medicines efficiently raise the levels of active GLP-1 and GIP by blocking DPP-4 activity. As a result, there is an increase in the production of insulin, a decrease in the release of glucagon, and a lowering of glucose levels after a meal. Multiple clinical trials have conclusively shown that DPP-4 inhibitors effectively lower glycated hemoglobin (HbA1c) levels. Certain studies have even proved their equivalent efficacy to other anti-diabetic medications such as metformin or sulfonylureas. Furthermore, DPP-4 inhibitors possess the benefit of being weight-neutral and exhibiting a little risk of hypoglycemia. These qualities render them a compelling option for patients with type 2 diabetes mellitus who are overweight or susceptible to hypoglycemia episodes. In general, DPP-4 inhibitors are a promising therapeutic choice for the management of type 2 diabetes mellitus (T2DM), offering effective regulation of blood sugar levels with a minimal likelihood of adverse effects. Nevertheless, it is important to acknowledge some restrictions and factors to take into account, including the possibility of heightened susceptibility to pancreatitis, nasopharyngitis, and certain drug-drug combinations. Additional investigation is necessary to completely clarify the long-term safety and potential supplementary advantages of DPP-4 inhibitors.

Keywords: Irritable Bowel Syndrome, Anxiety, Academic performance, mental health, Quality-of-Life, Undergraduate

Significance | To establish potential DPP-4 inhibitors.

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1. Introduction

Dipeptidyl peptidase-4 inhibitors are a type of medication used to manage high blood sugar levels in individuals with type 2 diabetes mellitus, a condition that significantly increases the likelihood of developing coronary disease, heart failure, stroke, and various other cardiovascular problems. DPP-4 inhibitors are orally administered drugs with a low molecular weight that efficiently and rapidly suppress the function of DPP-4 (Gilbert and Pratley, 2020).

DPP-4 inhibition results in a 2-3 times higher concentration of GLP-1 in the blood after a meal. This rise in GLP-1 is responsible for the glucose-dependent stimulation of insulin release and the suppression of glucagon release. DPP-4, an enzyme present in the circulation and expressed on the surface of several cell types, has been demonstrated to deactivate GLP-1 and GIP (Gallwitz, 2019). Serine protease DPP-4 regulates the bioactivity of several hormones, neuropeptides, and chemokines, including incretin

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hormones. According to Li et al., (2018), DPP-4 inhibitors promote postprandial insulin secretion by amplifying the impact of incretin hormones like GLP-1 and GIP.

DPP-4 can inactivate glucagon-like peptide 1 (GLP-1) by breaking peptide links. By inhibiting DPP-4, the concentration of active GLP-1 can be increased, resulting in enhanced insulin secretion and reduced HbAlc levels. This can be achieved without causing weight gain and with minimal risk of hypoglycemia (Fuh, et al., 2021).

DPP-4 inhibitors have the potential to decrease HbA1c levels by around 0.5 to 1 unit. The reduction in HbA1c levels, similar to other drugs used to lower blood sugar, is mostly influenced by the characteristics of the patients being investigated, their initial blood sugar levels, and the other treatments they get, such as lifestyle changes (Esposito et al., 2015).

These molecules have beneficial effects on the heart, kidneys, and blood vessels by reducing blood pressure, inflammation, cell death, and modulating the immune system. These actions are not related to the incretin pathway (Fuh, et al., 2021).

DPP-4 inhibitors showed comparable efficacy to metformin or pioglitazone in those who did not achieve their glycemic goals with non-pharmacological interventions. The primary and extensively employed application of DPP-4 inhibitors is as an adjunctive therapy in those who have inadequate glycemic control with metformin alone. Due to these circumstances and for this specific cause, a considerably greater percentage of patients attain the glycemic goal of HbA1c (7.0%) without experiencing hypoglycemia or weight gain when compared to a combination of metformin and sulfonylureas.

Patients taking this medicine combination can safely employ a variety of fixed dosage combinations of DPP-4 inhibitors with metformin, particularly when a reduction in the daily pill dose is required. Conversely, DPP-4 inhibitors can be utilized with oral treatment based on SGLT-2 inhibitors (either in conjunction with metformin when it is not recommended or well-tolerated, or as part of triple therapy with metformin). DPP-4 inhibitors can be utilized alongside injectable diabetic medication, including insulin. The combined treatment showed a further decrease in HbA1c levels by 0.5 to 0.7 %, along with a reduced occurrence of hypoglycemia episodes (Cho et al., 2018). Some important clinical advantages/benefits of DPP-4 inhibitors are as mentioned in **Figure 1** (Saini et al., 2023).

1. Advancement of DPP-4 Inhibitors

During the 1990s, researchers discovered orally active inhibitors that target the catalytic site of DPP-4, which were then used for initial *in-vivo* studies. DPP-4 inhibitors are small molecules that enter the catalytic pocket of DPP-4's dimeric structure and attach to the catalytic site, thereby inhibiting proteolytic activity. Certain DPP-4 inhibitors function as DPP-4 substrates, whereas others attach to the catalytic site without undergoing degradation. Valine pyrrolidide was an early example of a DPP-4 inhibitor, which served as a model for inhibiting DPP-4. Valine-pyrrolidide was demonstrated in 1995 to reduce glucose fluctuations after an oral glucose intake in cynomolgus monkeys and rats. Furthermore, in anesthetized pigs, the administration of Valine-pyrrolidide resulted in an increase in the concentration of intact GLP-1, prolonged the half-life of GLP-1 from 1 to 3 minutes, and augmented the insulin response to intravenous GLP-1 injection. Valine pyrrolidide was demonstrated to elevate the level of intact GIP, prolong the duration of GIP from 3 to 8 minutes, and enhance GIP's ability to stimulate insulin production. As a result, there was an increase in glucose removal and a decrease in the fluctuation of glucose levels following the administration of intravenous glucose in anesthetized pigs. The impact of Valine-pyrrolidide on glucose-intolerant mice fed a high-fat diet was also examined in the presence of a gastric glucose injection. Valine pyrrolidide was demonstrated to accelerate the increases in plasma GLP-1 and insulin levels after gastric glucose intake and improve glucose tolerance. However, Valine-pyrrolidide did not have any impact on the generation of insulin induced by glucose in isolated islets. These findings indicate that the main mechanism by which DPP-4 inhibition exerts its effects is through the prevention of inactivation of incretin hormones. Additional DPP-4 inhibitors were identified and subjected to testing during the 1990s. The DPP-4 inhibitor isoleucin-thiazolidide was observed to improve insulin production and glucose tolerance in both lean and obese Zucker rats. Additionally, it was found to prolong the half-life of GLP1 (Ahrén, 2005).

Two dipeptide analogs containing methanoprolinenitrile and exhibiting DPP-4 inhibitory properties were found to reduce glucose levels in Zucker rats. This research offered substantial evidence supporting the premise that inhibiting DPP-4 could be beneficial in reducing glucose levels. Additionally, the animal experiments established the foundation for further testing this concept in humans (Ahrén, 2019).

2. Currently available DPP-4 inhibitors:

Some important DPP-4 inhibitors available in the market are Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin, Linagliptin, Denagliptin, Dutogliptin and Omarigliptin. Sitagliptin is the initial commercially available specific inhibitor of DPP-4, succeeded by Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin. These drugs share the same mechanism of action, however, the different gliptins exhibit variations in their pharmacodynamics and pharmacokinetic characteristics. The primary distinctions among them encompass their potency, target specificity, oral absorption rate, duration of elimination, affinity for plasma proteins,

metabolic pathways, production of active metabolites, primary routes of excretion, dosage modification for renal and hepatic impairment, and potential interactions with other drugs (Makrilakis, 2019). The bioavailability of DPP-4 inhibitors is high, and their pharmacologic and pharmacokinetic features lead to effective inhibition of DPP-4 with once-daily doses (except for vildagliptin, which requires twice-daily dosing). Omarigliptin is a DPP-4 inhibitor that has a lengthy duration of action and is used once a week (Gallwitz, 2019). The structural details of some identified and under-research DPP-4 inhibitors are discussed in **Figure 2**. **Table 1** displays a comparison of some important DPP4 inhibitors currently available in the market (Florentin et al., 2022; Deacon and Holst, 2013; Baetta and Corsini, 2011; Ceriello et al., 2014).

***Sitagliptin*:**

Sitagliptin is an orally administered DPP-4 inhibitor. The FDA has approved it as monotherapy for diabetic treatment, but it can also be used in combination with metformin or glitazone if metformin plus diet fails to achieve the desired outcomes. In Europe, Sitagliptin monotherapy is mostly prescribed for those who have just been diagnosed with diabetes mellitus or for those who have not responded well to other oral hypoglycemic drugs. According to certain publications, Sitagliptin is compatible with metformin, glitazone, a sulfonylurea, or can be used in a triple combination with metformin and a sulfonylurea. However, it is not compatible with glinides. Research has demonstrated that the concurrent administration of Sitagliptin and metformin enhances the functionality of pancreatic β-cells. When given by itself, Sitagliptin can effectively inhibit DPP-4 activity, reducing it by 96% after 2 hours and by 80% after 24 hours. Administering a single dose of Sitagliptin orally was observed to significantly enhance the GLP-1 response during an oral glucose tolerance test, leading to a substantial reduction in blood glucose levels. Sitagliptin improves glycemic control in individuals with type 2 diabetes by increasing plasma insulin and C-peptide levels, while reducing plasma glucagon levels (Lotfy et al., 2011; Karasik et al., 2008).

***Saxagliptin*:**

Saxagliptin is a newly developed drug by Bristol-Myers Squibb and AstraZeneca. It is a selective and reversible inhibitor of DPP-4, specifically designed to treat type 2 diabetes. Onglyza, a drug known as Saxagliptin, received FDA approval on July 31, 2009. This DPP-4 inhibitor is remarkably potent, exhibiting around ten-fold more efficacy compared to Vildagliptin or Sitagliptin. Based on the clinical inquiry, Saxagliptin can reduce the manifestations and indications of diabetes mellitus. When used daily, it possesses the ability to reduce HbA1c levels. Saxagliptin dramatically decreased both fasting and postprandial blood glucose levels. Oral Saxagliptin at doses of 2.5-10 mg per day, when used with metformin, led to a significant decrease in HbA1c levels compared to a placebo. Saxagliptin has shown a considerable reduction in blood glucose levels when compared to a placebo. Patients have exhibited good tolerance to Saxagliptin since it does not cause significant hypoglycemia. Saxagliptin has a negligible impact on weight (Tahrani et al., 2009).

***Vildagliptin*:**

Vildagliptin, sold under the brand name Galvus, obtained its license as the second DPP-4 inhibitor for the treatment of diabetes mellitus in the European Union in 2008. Sitagliptin and Vildagliptin possess unique chemical compositions and exhibit different patterns of drug absorption, distribution, metabolism, and elimination. Sitagliptin functions as a DPP-4 competitive antagonist, while Vildagliptin and Saxagliptin act as DPP-4 substrates, inhibiting the target molecule. Vildagliptin exhibits a high affinity for DPP-4. Due to its strong attraction, Vildagliptin can lead to substantial reductions in the plasma HbA1c level among individuals with type 2 diabetes. In addition, Vildagliptin enhances both fasting and postprandial GLP-1 levels, while also improving the sensitivity of pancreatic β-cells to glucose and insulin. Additionally, it can significantly reduce postprandial lipaemia. Vildagliptin, unlike most other DPP-4 inhibitors, does not impede the gastric emptying process. While Vildagliptin does improve pancreatic β-cell function in patients with type 2 diabetes mellitus (T2DM), it has minimal impact on weight gain. Patients who were administered Vildagliptin exhibited notably reduced plasma concentrations of proinsulin, which is indicative of impaired β-cell function. Vildagliptin can reduce the breakdown of fats (lipolysis) and the increase in triglyceride levels after a meal (postprandial hypertriglyceridemia). This is likely because vildagliptin increases the levels of a hormone called incretin in the blood, which has been proven to restrict the absorption of triglycerides in the intestines (He, 2012, Keating, 2010).

Alogliptin

It was developed by Takeda Pharmaceutical Company in Japan, and is a DPP-4 antagonist classified as a quinazolinone. Research has determined that between 45% and 88% of orally ingested Alogliptin is available for biological activity. Several studies investigating the impact of Alogliptin on individuals with diabetes have shown that it can restore glycemic levels to a normal range (Keating, 2015; Andukuri et al., 2009).

Linagliptin

It is a xanthine derivative that has a high ability to detach DPP-4 at a very slow speed. Initial investigation has indicated that Linagliptin exhibits a strong affinity for its main target molecule even at low levels in the bloodstream, rendering it a suitable medicine. Compared to other DPP-4 inhibitors, this medication has a longer duration of effect in living organisms, making it suitable for once-daily use as an anti-diabetic drug. Individuals with a busy schedule will find it advantageous to participate in a

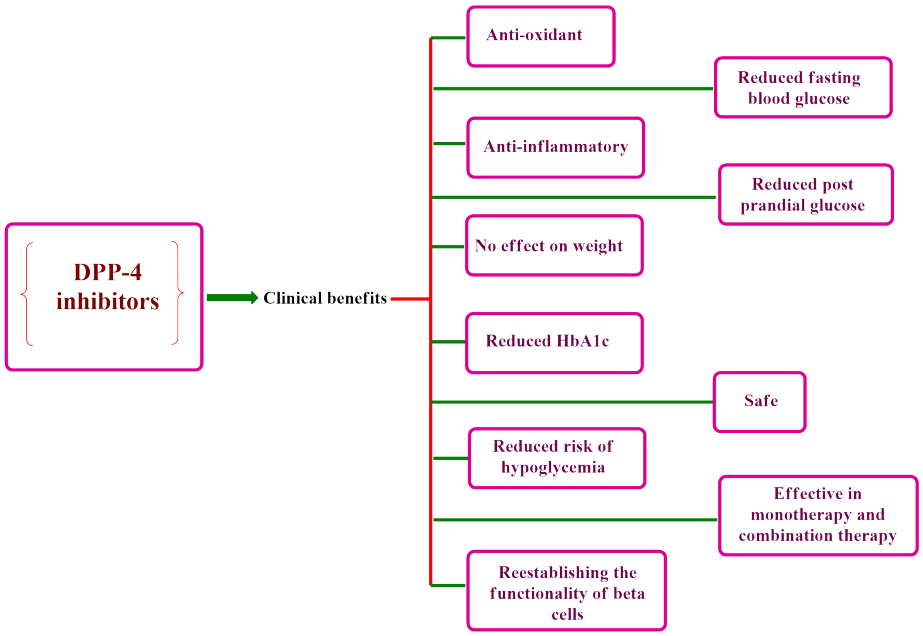

Figure 1. Principal Clinical benefits of DPP-4 inhibitors in therapeutic management.

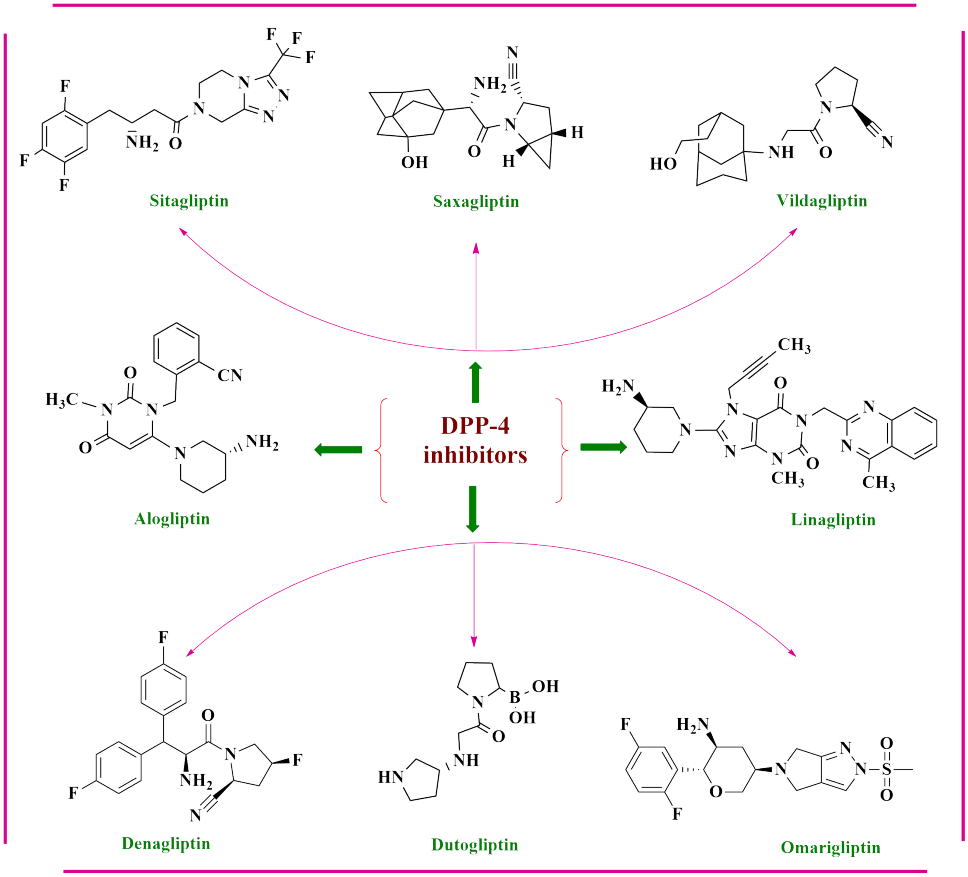

Figure 2. Chemical structures of some reported potential DPP-4 inhibitors.

Table 1. An analysis of some of the DPP-4 inhibitors that are currently on the market.

Drug	Dosage Forms	Excretion	DPP-4 Inhibition	Half-Life (Hours)	Metabolism	Fixed dose combinations
Sitagliptin	25mg 50mg 100mg	renal (~80% unchanged as parent)	Max ~97%; >80% 24 h post-dose	8–24	Not appreciable	With Metformin, With Simvastatin
Saxagliptin	2.5mg 5mg	Renal (12–29% as a parent, 21–52% as metabolite)	Max ~80%; ~70% 24 h post-dose	2–4 (parent) 3–7 (metabolite)	Hepatically metabolized to active metabolite	With metformin, With dapagliflozin
Vildagliptin	50mg	Renal (22% as parent, 55% as primary metabolite)	Max ~95%; >80% 12 h post-dose	1(1\2)–4(1\2)	Hydrolyzed to inactive metabolite	With metformin
Alogliptin	6.25mg 12.5mg 25mg	Renal (>70% unchanged as a parent)	Max ~90%; ~75% 24 h post-dose	12–21	Not appreciably	With metformin, With pioglitazone
Linagliptin	5mg	Biliary (>70% unchanged as parent); <6% via kidney	Max ~80%; ~70% 24 h post-dose	10-40	Not appreciably	With metformin, With empagliflozin

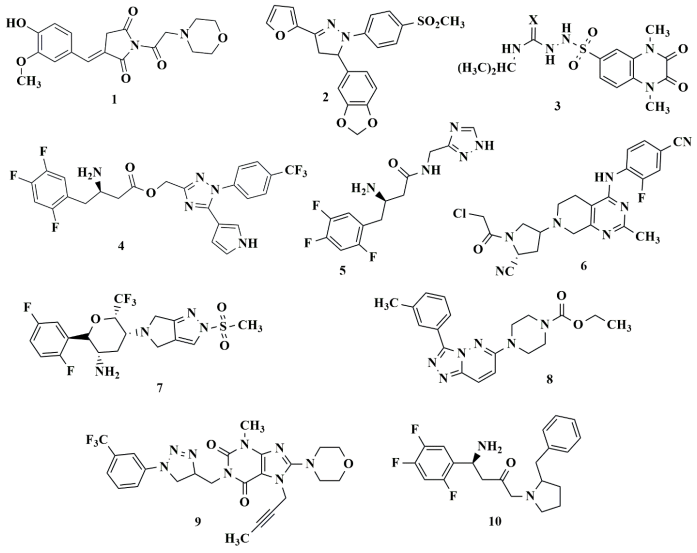

Figure 3. Chemical structures of synthesized DPP-4 inhibitors 1-10.

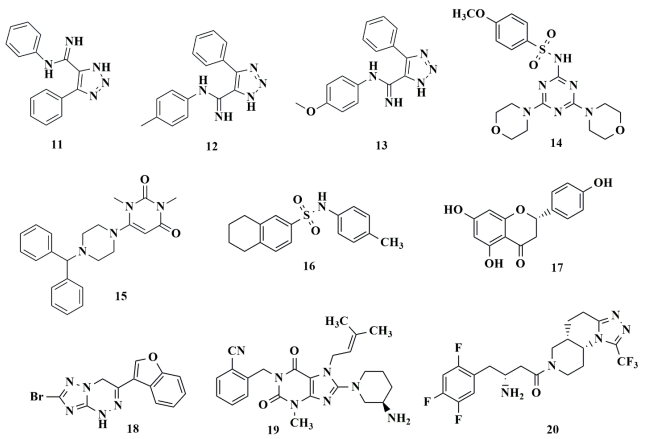

Figure 4. Chemical structures of synthesized DPP-4 inhibitors 11-20.

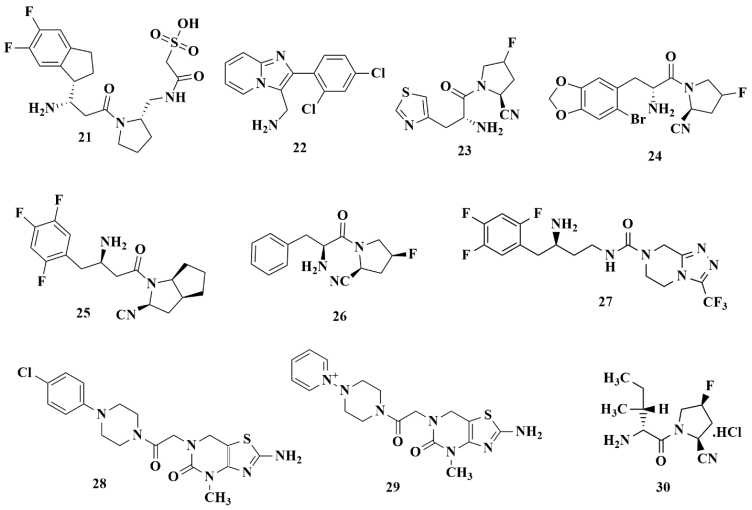

Figure 5. Chemical structures of synthesized DPP-4 inhibitors 21-30.

program that just requires their attention once each day. While it does increase basal GLP-1 levels, it does not significantly impact plasma insulin concentration 24 hours after delivery. At therapeutic dosage, it has been proven to inhibit DPP-4 by over 80% (Graefe-Mody et al., 2012; Sortino et al., 2013).

Denagliptin

It was manufactured by Glaxo Smith Kline and has shown notable variations in its pharmacokinetics, side effects, and therapeutic efficacy in comparison to the already accessible DPP-4 inhibitors like Vildagliptin and Saxagliptin. This could be associated with the presence of supplementary fluoride molecules in Denagliptin. Denagliptin is now in the experimental phase and has not yet received approval for clinical usage (Kumar et al., 2021).

Dutogliptin

It is a water soluble DPP-4 inhibitor that is excreted unchanged in urine and has a long half-life of 10 to 13 hours. In comparison to Vildagliptin, this is a more recent compound that has the ability to inhibit DPP-4 for a prolonged duration (Johnson, 2010).

Omarigliptin

This is a weekly administered DPP-4 inhibitor with possible long-acting effects, used to treat diabetes mellitus. The mechanism of action involves the inhibition of incretins, suppression of glucagon release, and enhancement of insulin release to regulate blood glucose levels (Mcintosh et al., 2005, Evans and Bain, 2016; Tan, 2016).

3. Synthetic Review of DPP-4 Inhibitors:

Huneif et al., (2022) devised a molecule by merging vanillin, thiazolidinedione, and morpholine. The objective of the intended study is to showcase the capacity of compound **1** to regulate many targets that contribute to hyperglycemia. The synthesized molecule exhibited significant inhibitory activity against α-glucosidase, α-amylase, and protein tyrosine phosphatase 1B, ranging from good to moderate. The compound demonstrated outstanding *in-vitro* inhibition of Dipeptidyl peptidase-4, with an IC_{50} value of 0.09 µM, in comparison to Ascorbic acid (IC_{50}=1.12 ± 1.09µM), which was used as a reference drug. The DPPH assay demonstrated the excellent potential of the substance in terms of its antioxidant activities. Through *in-vivo* investigations, it was demonstrated that compound **1** exhibited a high level of safety in experimental mice. The compound's activity profile was monitored over 21 days, revealing its efficacy in experimental mice as well. Temel et al. (2022) reported the synthesis of three pyrazoline derivatives and assessed their inhibitory effects on dipeptidyl peptidase. Pyrazoline-based molecules were synthesized by reacting 1-(2-furyl)-3-(1,3-benzodioxol-5-yl)-2-propen with appropriate reagents. The compound is a phenylhydrazine hydrochloride with a substitution on the fourth position. Compound **2** had the most potent DPP-4 inhibitory effects, with an IC_{50} value of 5.75 ± 0.35 µM, surpassing the DPP-4 inhibitory activity of Sitagliptin (IC_{50}=0.019 ± 0.001 µM). Furthermore, compound **2** did not exhibit any noteworthy cytotoxic effects on L929 cells, and it was determined to be the most potent compound. Syam, et al., (2021) described the design and synthesis of a novel group of compounds containing 1,4-dimethyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide. The assessment indicated that the majority of the novel compounds appeared as selective dipeptidyl peptidase-4 inhibitors and *in-vivo* hypoglycemic agents. The compound's safety profile was established through an examination of its acute toxicity. Compound **3** demonstrated compliance with Lipinski's rule, suggesting that it has good potential for being absorbed orally. Compound **3** exhibited a significant level of selectivity in inhibiting DPP-4, with a potency that was more than 1000 times greater than its inhibition of DPP-8/9. The molecule was evaluated as a potential *in-vivo* hypoglycemic agent and showed a favorable glucose-controlling effect when compared to linagliptin, a reference medicine. In addition, the molecule exhibited a favorable safety profile towards healthy cells, with an IC_{50} value of 9.30 µM, as compared to Linagliptin (IC_{50} = 0.77 ± 0.0085 nM), which was used as a reference medication. Fuh, et al., (2021) produced four sets of 1,2,4-triazole derivatives using N,O-disubstituted glycolamide, N,N′-disubstituted glycinamide, β-amino ester, and β-amino amide as linkers. These compounds were created to develop novel inhibitors for dipeptidyl peptidase-4. Compounds **4** and **5**, with IC_{50} values of 49.9 nM and 50.4 nM respectively, showed potential as lead compounds for the development of DPP-4 inhibitors. In comparison, the reference medication Sitagliptin has an IC_{50} value of 28 nM. Their *in-vitro* activity was commendable, displaying outstanding selectivity. Consequently, they hold great potential as a prospective candidate for the treatment of diabetes mellitus. Fang, et al., (2020) developed a set of tetrahydropyridopyrimidine compounds as DPP4 modulators that have hypoglycemic action. Seven fragments derived from DPP-4 inhibitors were combined with the tetrahydropyridopyrimidine scaffold by hybridization. Compound **6** exhibited the highest level of activity, with an IC_{50} value of 8.7 nM, and a substantial inhibition rate of 74.5% against DPP-4 at a concentration of 10 µM. In addition, the blood glucose levels decreased by 19.5% during the oral glucose tolerance test when administered at a dose of 30 mg/kg. This reduction was more pronounced compared to vildagliptin, which resulted in a 16.4% decrease at the same dose. Zhang, et al., (2020) developed a new collection of tetrahydropyran derivatives with trifluoromethyl substitution. These derivatives were found to be highly effective in inhibiting DPP-4 and demonstrated a much longer duration of action compared to currently available DPP-4 inhibitors in the market. Compound **7** demonstrated exceptional effectiveness and

a favorable safety profile, with an IC_{50} value of 4.2 ± 0.5 nM. This is in comparison to Omarigliptin, a reference medication, which has an IC_{50} value of 3.1 ± 0.37 nM. Bindu et al., (2020) conducted the synthesis and evaluation of a group of 12 piperazines substituted with triazolo-pyridazine-6-yl. The DPP-4 inhibitory capability of these compounds was assessed using in-silico and *in-vitro* testing, in addition to evaluating their insulinotropic actions in cells. The target compounds exhibited significant inhibitory potential as demonstrated by the findings of molecular docking and ELISA-based enzyme inhibition experiments. The MTT assay results demonstrated that a dose of 2.5 nM (with an IC_{50} of 1.25 nM) was the highest dose that could be utilized. Any dosage over this level was found to be essential for the cells, as compared to Linagliptin (with an IC_{50} of 1.25 ± 0.02 nM), which served as the reference standard. Compound **8** exhibited exceptional antioxidant and insulinotropic action, achieving a remarkable efficacy of 99%. Moreover, it demonstrated significant effectiveness *in-silico* and *in-vitro* for the intended biological activities. Narsimha et al. (2020) developed and assessed a collection of new xanthine derivatives containing 1,2,3-triazole for their dipeptidyl peptidase-4 activity in laboratory conditions. Compound **9** had a remarkable inhibitory action against DPP-4, with an IC_{50} value of 16.34 nM and an inhibitory rate of 78.53%. This activity was compared to that of Alogliptin, a reference drug, which had an IC_{50} value of 6.28 nM. The structure-activity relationship (SAR) of this xanthine derivative proved valuable in the development of new dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes. Mehanna and Kelada (2020) reported novel compounds intended for investigating the impact of substituting the 2-benzyl-piperazine ring system of a previously identified powerful DPP4 inhibitor, with piperidine and pyrrolidine heterocyclic ring systems. The reported DPP4 inhibitor exhibited an IC_{50} value of 19 nM. The study found that replacing the piperazine ring of the lead molecule with a smaller pyrrolidine ring, while keeping the benzyl substitution at the 2-position, led to the most potent inhibitor (compound **10**), as indicated by its increased activity (**Figure 3**).

Dastjerdi et al. (2020) designed and synthesized a series of 1,2,3-triazole-5-carboximidamide derivatives as evaluated for potential DPP-4 inhibition using Sitagliptin as the standard drug. Compounds **11**, **12,** and **13** presented desirable DPP-4 inhibition with IC^{50} values of 14.75 nM, 6.75 nM, and 6.57 nM in comparison to Sitagliptin which yielded 16.39 nM inhibition. Compound **11** appeared as the most potential derivative with a significant reduction in glucose level during the OGTT test. Also, compound 11 has produced significant anti-hyperglycemic results with no signs of hypoglycemia at a daily dose of 10 mg/Kg. Wang et al. (2019) developed a new set of di-morpholine 1,3,5-triazine derivatives to create an antidiabetic drug that works by inhibiting dipeptidyl peptidase-4 and then evaluated for their ability to block DPP iso-enzymes, including DPP-4, DPP-8, and DPP-9. The *in-vitro* inhibition assay indicated that these compounds effectively and specifically inhibit DPP-4, with a greater affinity for DPP-4 compared to DPP-8 and DPP-9. These compounds exhibited no cardiotoxicity, as evidenced by their lack of action against human cardiac ion channels. The investigation revealed that compound **14** is the most powerful inhibitor of DPP-4, with an IC_{50} of 1.10 nmol/L, in comparison to the conventional Alogliptin, which has an IC_{50} of 3.22 nmol/L. Compound **14** underwent additional assessment to determine its effectiveness in an oral glucose tolerance test (OGTT) which demonstrated a dose-dependent enhancement of glucose tolerance, reaching its peak at a dosage of 30 mg/kg. It also demonstrated a decrease in the area under the curve from 0 to 120 minutes, which was comparable to the effects of Alogliptin. Compound **14** induced a decrease in blood glucose levels, total cholesterol, triglyceride, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) in Wistar rats, as compared to the diabetic control group. Conversely, the level of high-density lipoprotein (HDL) was observed to be raised. Compound **14** enhanced the antioxidant potential by increasing the activity of superoxide dismutase, catalase, and glutathione peroxidase while decreasing the level of malondialdehyde when compared to the normal control group. Jha and Bhadoriya (2018) have prepared N-methylated and N-benzylated pyrimidinedione derivatives and assessed them for *in-vitro* DPP-4 inhibition against Alogliptin as the standard drug. Compound **15** appeared as the most potential derivative with 29.73 % inhibition at a concentration of 10 $\mu molL^{-1}$. Abd El-Karim, et al., (2018) prepared a novel series of tetralin-sulfonamide derivatives as dipeptidyl peptidase-4 inhibitors. Compound **16** exhibited an IC_{50} value of 2.80 nM, demonstrating a selectivity of 20-40 times greater than DPP-8 and DPP-9 in comparison to Sitagliptin (IC_{50} = 15.63 ± 0.0085 nM), which was used as a reference drug. The preparation of the compound **16** complex was successfully achieved with a high labeling yield of around 90% utilizing chloramine-T as the oxidizing agent and was chosen as a highly effective derivative with strong DPP-4 inhibition and hypoglycemic properties. Li, et al., (2018) developed and assessed a range of new pyrimidinedione derivatives to determine their effectiveness in inhibiting dipeptidyl peptidase-4 in laboratory settings and their ability to reduce high blood sugar levels in living organisms. Compound **17** exhibited a highly effective inhibitory activity against DPP-4, with an IC_{50} value of 64.47 nM. This result was compared to the IC_{50} value of 37.96 nM for Sitagliptin, which was used as a reference standard. Subsequent investigations demonstrated that compound **17** exhibited promising *in-vivo* hypoglycemic activity. The structure-

activity correlations of these pyrimidinedione derivatives could be valuable in the development of new DPP-4 inhibitors for the treatment of type 2 diabetes. Patel, et al., (2017) developed new DPP-4 inhibitors using triazolo[5,1-c] [1,2,4]triazine derivatives and tested them for their ability to inhibit DPP-4. Compound **18**, which showed a promising potential, exhibited an IC_{50} value of 28.05 μM against DPP-4, with a selectivity of 8-10 times greater than that of DPP-8 and DPP-9 in comparison to Sitagliptin, a reference drug with an IC_{50} value of 0.018 μM. Compound **18** demonstrated a dose-dependent reduction in blood glucose excursion during the Oral Glucose Tolerance Test (OGTT). Administration of this compound over 28 days resulted in a significant improvement in serum glucose levels in individuals with type 2 diabetes. Ran et al., (2016) has prepared, evaluated and carried out molecular docking analysis of (R)-2-((8-(3-aminopiperidin-1-yl)-3-methyl-7-(3-methylbut-2-en-1-yl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)methyl)benzo -nitrile as Dipeptidyl Peptidase-4 Inhibitors. The inhibitor with the highest potency is compound **19**, with an IC_{50} value of 23.5 nM. It showed a moderate level of antihyperglycemic activity when compared to the standard antidiabetic drug Linagliptin in OGTT. Furthermore, the pathogenic condition of DIO mice was significantly ameliorated. The molecular docking studies provided a clear understanding of the strong binding affinity between compound **19** and the active site of DPP-4. Schwehm et al., (2015) prepared substituted ring-fused 1,2,4-triazole derivatives. They replaced the piperazine fused 1,2,4-triazolo group found in Sitagliptin with a different tricyclic octahydro-[1,2,4]triazolo[4,3-a][1,6]naphthyridine molecular structure in order to produce hybrid structures. Compound **20** exhibited DPP-4 inhibitory activity at a level of IC_{50} 28 nM, in comparison to Sitagliptin's with IC_{50} of 22 ± 2 nM (**Figure 4**).

Jiang et al., (2015) reported β-homophenylalanine compounds that act as inhibitors of dipeptidyl peptidase-4. Incorporating a sulfamine group at the *meta* position of the phenyl ring resulted in a significant enhancement in potency against DPP-4, with a 6 to 12-fold increase. Compound **21** exhibited DPP-4 inhibitory activity, with an IC_{50} value of 0.87 nM, in comparison to Sitagliptin, a reference drug, which had an IC_{50} value of 19.0 nM. Meanwhile, studies conducted showed that compound **21** had a similar effectiveness to Sitagliptin when administered at a dosage of 10 mg/kg. Li et al., (2015) developed a novel set of DPP-4 inhibitors using a scaffold hopping technique and docking studies, by incorporating an imidazo[1,2-a]pyridine scaffold. Findings demonstrated that compound **22** had high potency (IC_{50} = 0.13μM), selectivity, and *in-vivo* efficacy as a DPP-4 inhibitor, when compared to Alogliptin (IC_{50} = 0.007 μM), which served as the reference standard. Compound **22** exhibited the essential binding characteristics of DPP-4 due to the presence of the pyridine component in the imidazo[1,2-a]pyridine ring, which also enables an extra interaction with DPP-4. Compound **22** showed potential as a viable candidate for the advancement of a new DPP-4 inhibitor for the treatment of T2DM. Ji et al., (2014) synthesized novel hetero-aromatic compounds through the modification of α-aminopyrrole-2-carbonitrile derivatives. The alterations were derived from the correlation between the structure and action of pyrrole-2-carbonitrile inhibitors. All compounds demonstrated substantial inhibitory effects on dipeptidyl peptidase-4. Compound **23** (IC_{50} = 0.004 mM) and compound **24** (IC_{50} = 0.01 mM) had significant inhibitory effects on DPP-4, indicating strong selectivity and effectiveness in an oral glucose tolerance test performed on ICR mice. Furthermore, they displayed limited pharmacokinetic properties. Ji et al., (2014) developed a range of α-amino pyrrole-2-carbonitrile derivatives. Compound **25** showed effectiveness and specificity as DPP-4 inhibitor, with an IC_{50} value of 0.004 ± 0.004 μM. It also demonstrated favorable selectivity against similar peptidases and displayed effective performance in oral glucose tolerance tests conducted on ICR mice. Additionally, it demonstrated moderate PK profiles when compared to Sitagliptin (with an IC_{50} value of 0.02 ± 0.06 μM), which was used as a reference drug. Furthermore, compound **25** demonstrated no blockade of the hERG channel and displayed no inhibitory effects on liver metabolic enzymes, such as CYP2C9. Wang et al. (2013) reported a new group of pyrrolidine-2-carbonitrile and 4-fluoropyrrolidine-2-carbonitrile compounds with the purpose of inhibiting dipeptidyl peptidase-4. Compound **26** appeared as a potent, secure, and specific inhibitor of DPP-4. *In-vivo* experiments demonstrated reduction in blood glucose levels in mice following an oral glucose test. Compound **26** exhibited potent inhibition of DPP-4 (IC_{50} = 0.017 μM), reasonable specificity towards DPP-4 in oral glucose tolerance tests when compared to Vildagliptin (IC_{50} = 0.020 μM), as a reference standard. Zhu et al. (2013) examined the intricate formations of DPP-4 found in the Protein Data Bank and developed a range of triazole compounds. Following enzyme activity testing and crystallographic verification of the binding interaction patterns, it was discovered that the triazole compounds possessed the ability to inhibit DPP-4 with IC_{50} values in the micromolar range. Tests were conducted on this series to assess the stability of liver microsomes and the metabolic activity of cytochrome P450. The results indicated unfavorable pharmacokinetic characteristics for the triazole compounds. In order to address this disadvantage, they replaced the triazole ring with either an amide or urea group, resulting in the development of a novel set of DPP-4 inhibitors. Compound **27** was chosen for further investigation of its *in-vivo* effects in mice using an oral glucose tolerance test, based on its enzyme activity, metabolic

stability, and selectivity over DPP-8 and DPP-9. The results indicated that compound **27** demonstrated comparable effectiveness to Sitagliptin when administered at a dosage of 3 mg/kg. This molecule exhibits a marginally reduced half-life compared to Sitagliptin, but a prolonged mean residence time relative to Sitagliptin. Additionally, it takes approximately four times longer than Sitagliptin to reach its maximal concentration in the bloodstream. This compound was recognized as a potential candidate for *in-vivo* investigation. Sharma et al. (2012) developed a series of thiazolopyrimidine compounds to assess their ability to inhibit Dipeptidyl Peptidase-4. Among all the compounds tested, Compound **28** (IC_{50} = 0.489 lM) and Compound **29** (IC_{50} = 0.329 lM), which includes a piperazine with a heterocyclic substitution and an acetamide linker, were shown to be the most effective inhibitors of DPP-4. Administration of a single dosage (10 mg/kg) of compounds **28** and **29** effectively decreased the rise in blood glucose levels during an oral glucose tolerance test in a rat model of diabetes caused by streptozotocin. Compound **29** has more potency than compound **28** because it possesses an extra hydrogen-bound contact involving the nitrogen atom of the pyridyl group. This is further supported by the superior electrostatic interaction energy of compound **29** as compared to compound **28**, despite compound **28** having a larger steric interaction energy. Fukushima et al. (2008) discovered that 2-cyano-4-fluoropyrrolidines are highly effective in inhibiting DPP-4 and have been making changes to the 1-position of pyrrolidine to develop even more beneficial inhibitors. A derivative of L-tert-butylglycine was shown to be a persistent and powerful inhibitor of DPP-4, which demonstrated a glucose-lowering action in living organisms. Compound **30** is anticipated to have utility as a therapeutic drug in reducing postprandial hyperglycemia and managing type 2 diabetes mellitus. Due to its superior inhibitory action and chemical stability profiles, it demonstrated the most desirable characteristics. Compound **30** could potentially prevent the deactivation of active GLP-1 by inhibiting DPP-4. This could lead to an increase in GLP-1 activity, which in turn could boost the production of insulin by acting on β-cells in the pancreas. As a result, hyperglycemia after glucose intake could be suppressed (**Figure 5**).

4. Discussion and expected outcomes

Recent advancements in incretin-based medical treatments offer a wide range of choices to regulate blood sugar levels for individuals with type 2 diabetes mellitus (T2DM) and have distinct benefits compared to traditional medications that reduce blood glucose levels. However, it is important to consider the probable expense of these therapies when evaluating their suitability for widespread clinical use. DPP-4 inhibitors are unquestionably pricier than sulphonylureas, although more economical than GLP-1 receptor agonists. Due to insufficient availability of data; more economic assessments are required to substantiate the transition from sulphonylureas to DPP-4 inhibitors along with their safety and effectiveness. This will aid in defining their function in the management of Type 2 Diabetes Mellitus (T2DM) while offering doctors vital insights to facilitate educated treatment choices. Furthermore, it is essential to determine the patient groups who are most likely to have positive outcomes with DPP-4 inhibitors to develop tailored treatment strategies. This may be accomplished by conducting continuous clinical trials and studying actual data. Additionally, more investigation is required to examine the possible advantages of combining DPP-4 inhibitors with other treatments that decrease blood glucose levels (Saini et al., 2023; Rollo et al., 2016). Implementing this approach might enhance overall glycemic regulation and mitigate the potential for negative consequences linked to elevated dosages of individual medications. In summary, ongoing investigation in the area of DPP-4 inhibitors shows potential for enhanced control of T2DM and more favorable results for patients.

5. Conclusion

DPP-4 inhibitors have demonstrated efficacy as antidiabetic medicines by enhancing glucose regulation through the stimulation of insulin production and suppression of glucagon secretion. These treatments are relatively safe, well-tolerated, and have fewer negative effects in comparison to other medications used to treat diabetes. In addition, DPP-4 inhibitors have demonstrated supplementary advantages, such as diminishing cardiovascular risks and inflammation. Nevertheless, they are not appropriate for every individual with diabetes and may not yield the desired results in patients with severe or later stages of the condition. Before administering DPP-4 inhibitors as antidiabetic medications, healthcare practitioners should take into account the individual's medical history, age, renal function, and any drug interactions.

Author contribution

M.J.N. developed Study design, wrote, reviewed, and edited the paper.

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Competing financial interests

The authors have no conflict of interest.

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