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BEYOND BLOOD SUGAR CONTROL: A COMPREHENSIVE REVIEW OF DPP-4 INHIBITORS AND THEIR EXPANDING LANDSCAPE

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Abstract-
Type 2 diabetes, a prevalent chronic condition marked by insulin resistance and impaired beta cell function, presents a significant healthcare challenge. This review examines the potential of DPP-4 inhibitors, a novel class of medications, in managing this condition. DPP-4 inhibitors function by blocking the dipeptidyl peptidase-4 (DPP-4) enzyme, leading to increased levels of the incretin hormones GLP-1 and GIP. These hormones stimulate insulin release and suppress glucagon production, ultimately lowering blood sugar. Their safety, tolerability, and low risk of hypoglycaemia make them an attractive treatment option. Currently, DPP-4 inhibitors are increasingly becoming first-line therapy, demonstrating efficacy in controlling blood sugar. However, long-term safety and their potential influence on immune function and susceptibility to COVID-19 require further investigation. This review delves into the latest research on DPP-4 inhibitors, exploring their mechanisms of action, clinical effectiveness, and safety profile. Additionally, it highlights areas for future research, considering long-term effects, potential risks, and emerging questions related to immune function and COVID-19. By offering a comprehensive overview of DPP-4 inhibitors, this review aims to inform healthcare professionals and researchers about their potential in managing type 2 diabetes and pave the way for future advancements in diabetes care.

Keywords- Type 2 diabetes, DPP-4 inhibitors, GLP-1, GIP, insulin resistance, beta cell function, hypoglycemia, safety, long-term effects, immune function, COVID-19.

1-Introduction

In the long-term course of type 2 diabetes, insulin resistance, reduced glucose tolerance, and eventually the disease itself develop gradually. One of the health issues with the fastest global growth is in order to maintain normoglycemia, pancreatic islet cells are initially able to adapt to increased insulin resistance by secreting more insulin. However, there is a steady reduction in cell function as the illness progresses. If the resulting hyperglycemia is not addressed, type 2 diabetes' crippling vascular consequences, such as retinopathy, end-stage renal disease, sneuropathy, and cardiovascular disease, may develop in the future. Since type 2 diabetes is a progressive condition, treatment must often be intensified over time. Traditional treatment plans often fall short of addressing the disease's progressive character, despite the fact that all current medications are typically successful in the short- to medium-term. Additionally, current treatments may be linked to an increased risk of hypoglycemia (with sulphonylureas and insulin), weight gain (with sulphonylureas, thiazolidinediones, and insulin),

and gastrointestinal intolerance (with metformin), which pose significant obstacles to achieving optimal glycaemic control (1). The control of plasma glucose levels involves a complex interplay of hormonal and neurological cues, in addition to insulin and glucagon, according to research on the pathophysiology of diabetes. However, the creation of incretin hormone analogues, substances that prevent them from degrading and so increase their concentration, and/or substances that bind to their receptors, may make it easier to attain ideal glycaemic control (2). Additionally, these treatments might focus on physiological flaws that aren't addressed by today's pharmaceuticals, or they could have an additive or cooperative mode of action with today's treatments. Current therapies often fail to maintain glycaemic control and might have unfavourable side effects, including weight gain and hypoglycaemia episodes. The enzyme dipeptidyl peptidase-4 is crucial for the metabolism of glucose. It is in charge of causing incretins like GLP-1 to degrade (3). DPP-4 inhibitors have therefore been key players in the development of new and more potent medications. One new strategy that seems promising for the treatment of type 2 diabetes is the discovery of DPP-4 inhibitors, which amplify the incretin hormones by blocking the enzyme responsible for their breakdown. The function of this enzyme is inhibited by a new generation of oral hypoglycemic dipeptidylpeptidase-4 inhibitors, which prolong the incretin effect in vivo (4). The DPP-4 enzyme is inhibited, extending and enhancing the incretins' activity, which is crucial for regulating insulin production and blood sugar levels (5). The history, development, and discovery of innovative oral antidiabetic drugs are discussed in this article.

2-History

Serine protease DPP-4 has been a hot topic of study ever since it was discovered in 1967. DPP-4 inhibitors have long been sought as a means of illuminating the enzyme's functional relevance. The early 1990s saw the characterization of the first inhibitors. Each inhibitor played a crucial role in establishing an early structure-activity link that will be used in later research. The inhibitors may be divided into two categories: those that engage covalently with DPP-4 and those that do not (6). Many DPP-4 inhibitors feature 5-membered heterocyclic rings that imitate proline, such as pyrrolidine, cyanopyrrolidine, thiazolidine, and cyanothiazolidine. DPP-4 is a dipeptidase that preferentially binds substrates that contain proline at the P1 position. Covalent bonds between these substances and Ser630 in the catalytic residue are frequent. Cyan pyrrolidines with a nitrile function group were first discovered by Zaria Pharmaceuticals researchers in 1994. It was thought that these compounds would produce an imidate with the catalytic serine (7). Additional DPP-4 inhibitors, including those lacking nitrile groups but with other serine-interacting patterns, such as boronic acids, phosphonates, or diacyl hydroxylamine’s, were also described at the same time. Due to the similarities between DPP-4 and prolyl oligopeptides, these substances were not as powerful and also suffered from chemical instability. In 1995, Ferring Pharmaceuticals released two cyanpyrrolidine DPP-4 inhibitors and sought patent protection on them. These substances showed enhanced chemical stability and good potency. Based on the discovery that N-methyl glycine is a DPP-4-identified N-terminal amino acid, Edwin B. Vill Hauer at Novartis began investigating N-substituted glycinyl-cyanopyrrolidines in 1995. The study of this novel class of cyanpyrrolidines quickly gained enormous popularity (8).
the next few years. Because Vaso peptidase inhibition is thought to increase the antidiabetic impact of DPP-4 inhibition by boosting insulin production, certain experiments using combination inhibitors of DPP-4 and Vaso peptidase have been reported. The N-substituent of the DPP-4 inhibitor connects to the Vaso peptidase-inhibiting motif (9).

3-Arrangement of DPP-4

The structural details of the binding site are revealed in great detail by the X-ray structures of DPP-4. DPP-4 inhibitors come in a wide variety of structures, which is not unexpected given the characteristics of the binding site:

1. For high-affinity small molecule binding, a large lipophilic pocket along with numerous exposed aromatic side chains is required (10).
2. A large solvent access makes it feasible to adjust the physico-chemical characteristics of the inhibitors, which leads to superior pharmacokinetic behaviour. The prolyl oligopeptide family

includes the transmembrane glycoprotein DPP-4, which has 766 amino acids. A cytoplasmic tail, a transmembrane region, and an extracellular portion make up its three components. The extracellular portion is separated between a catalytic domain and an eight-bladed propeller domain, with the catalytic triad Ser630, Asp708, and His740 located in the catalytic domain. Tyr631, Val656, Trp662, Tyr666, and Val711 make up the side chains of the S1-pocket, which is very hydrophobic. The S1-pocket has a high degree of selectivity for proline residues, as shown by the fact that there are few differences in the pocket's size and shape in existing X-ray structures (11).

4-Bind point

The hydroxyl of the catalytic serine at the active binding site may interact with an electrophilic group that is often present in DPP-4 inhibitors **(Fig. 1).** The group in question is often a nitrile group; however, it might alternatively be boronic acid or diphenyl phosphonate. Due to interactions with the free amino group of the P2-amino acid, this electrophilic group may connect to the imidate complex with covalent bonds and slow, tight-binding kinetics, but it can also cause stability problems. Since these compounds have an affinity for other dipeptidyl peptidases, including DPP-2, DPP-8, and DPP-9, they have exhibited toxicity. As a result, inhibitors lacking the electrophilic group have also been produced (12). DPP-4 inhibitors come in a range of structural forms. A proline-mimetic cyan pyrrolidine P1 group was present in just a small number of the most powerful drugs in 2007. This group increases potency, most likely because the active site Ser 630 hydroxyl briefly covalently traps the nitrile group, delaying dissociation and causing certain inhibitors to bind slowly and tightly. When these potency increases were realised, several problems with chemical stability were discovered, necessitating the creation of more sophisticated compounds. It was looked into if it was possible to omit the nitrile group in order to prevent these stability problems. Aryl or polar side chains did not significantly inhibit DPP-4 in amino acids, and all compounds in this study without the nitrile group lost 20 to 50 times as much efficacy as those with the nitrile group did (13).

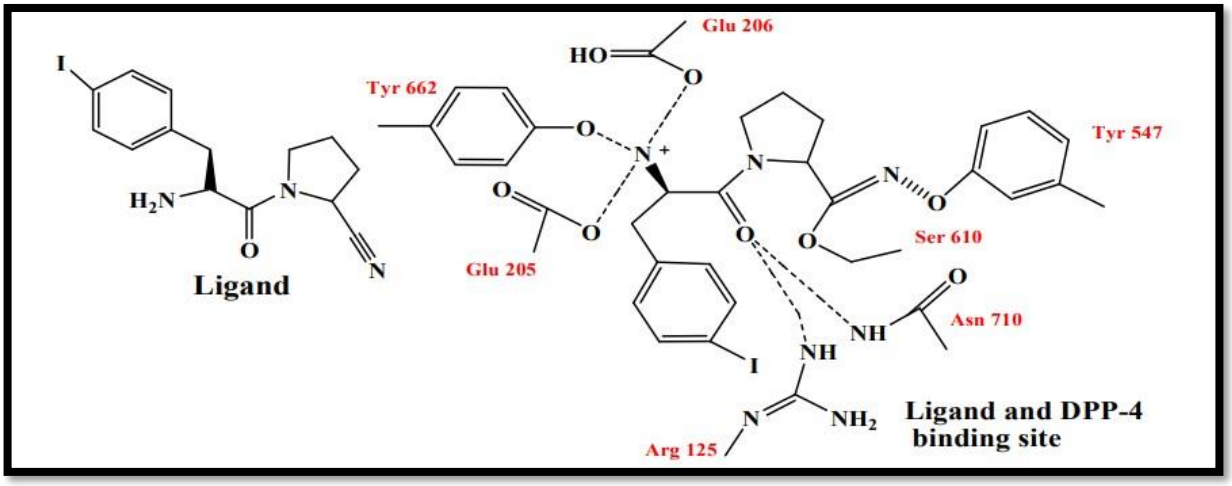

Figure 1: ligand-DPP-4 complex interactions that are important. A hydrogen bonding network is formed by the basic amine of the ligand. An imidate adduct is created when the nitrile combines with the catalytic active serine.

5-Finding and Creating DPP-4 Inhibitors

Finding a quick and precise method to develop novel DPP-4 inhibitors with suitable therapeutic characteristics is crucial. Virtual screening (VS) may provide greater rates of inhibitor identification than high-throughput screening (HTS), which often has poor hit rates. For instance, VS has been used to find fragments that might be inserted into the S1 and S2 sites of DPP-4 by screening for tiny primary aliphatic amines. On the other hand, these pieces weren't particularly effective; therefore, they were chosen as a place to start when creating better ones. A helpful technique for creating new DPP-4 inhibitors is 3D modelling. Based on the essential chemical characteristics of substances with DPP-4

inhibitory action, pharmacophore models have been created. These models may provide a fictitious representation of the key chemical component causing inhibitory action. Due to their limited selectivity, the earliest DPP-4 inhibitors were reversible and had undesirable side effects. Researchers hypothesised that in order to reduce potential negative effects, inhibitors with short half-lives would be preferable. However, the most recent DPP-4 inhibitors have had a long-lasting impact since clinical research has shown the contrary. P32/98 from Merck was one of the first DPP-4 inhibitors to be published. It is the first DPP-4 inhibitor to have effects in both animals and people, using thiazolidine as the P1-substitute. DPP-728 from Novartis, which uses 2-cyanopyrrolidine as the P1-substitute, is another vintage inhibitor. The potency is often increased by the inclusion of the cyano group. DPP-4 inhibitors are often either substrate-like or non-substrate-like in nature (14).

6-DPP-4 inhibitors' mode of action

Dipeptidyl-peptidase-4 (DPP-4) inhibitors, also known as "gliptins," are a class of oral anti-hyperglycemic medications that prevent the "incretin" hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) from becoming inactive. This affects glucose control through a number of mechanisms, including increased glucose-dependent insulin secretion **(Fig. 2).** In the present publication, their function in the management of T2D will be discussed, with a focus on their therapeutic efficacy and mechanism of action.

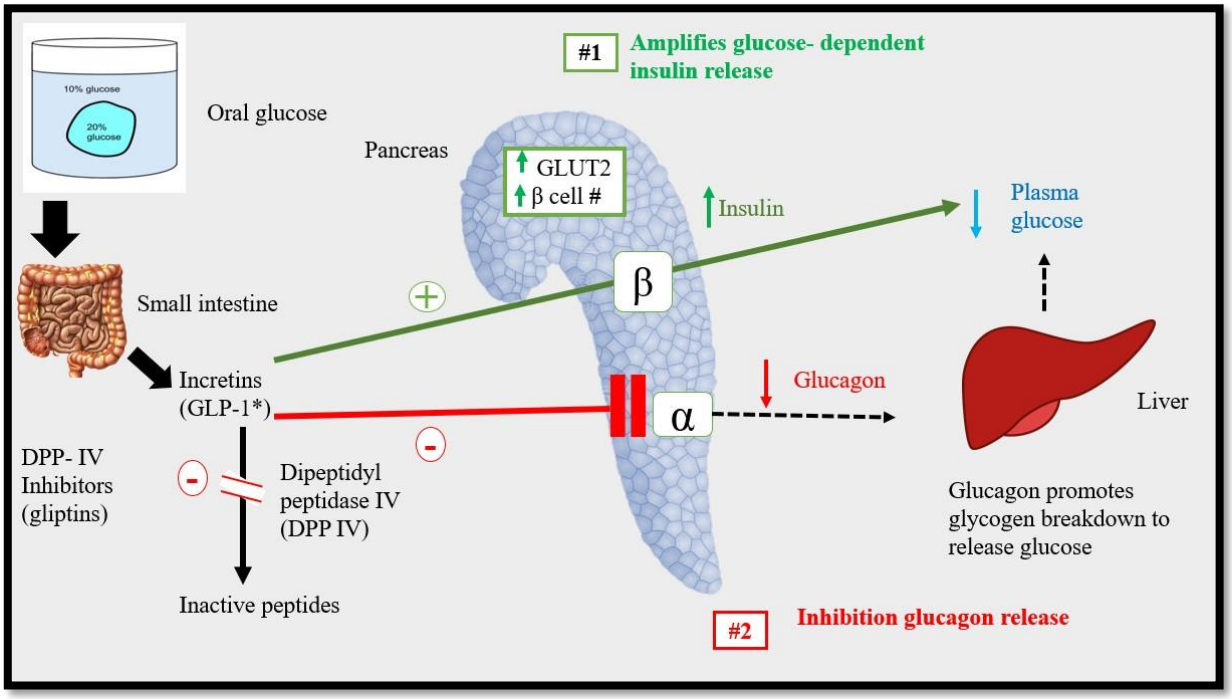

Figure 2. Function of DPP-4 and how DPP-4 inhibitors work.

7-DPP-4 blockers

7.1-INCRETINS

When glucose levels in the two situations are equal, the rise in plasma levels of insulin after oral glucose delivery is greater than the rise after intravenous glucose administration (16). This is known as the incretin effect, which is caused by intestinal hormones that are produced after consuming glucose and that increase the production of insulin. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two most significant incretin hormones (17). The incretin hormones are thought to provide more than 70% of the insulin response to an oral glucose challenge (18). The combination of diminished GLP-1 secretion and ineffective GIP action reduces the incretin impact in type-2 diabetes (19).

GIP is a 42-amino-acid peptide that is mostly generated by the K cells, which are primarily found in the duodenum (20). Following a meal, GIP is released into the bloodstream; the primary stimulators

seem to be fat and carbs, with protein playing a less significant role (21). On the other hand, L cells, which are mostly found in the bottom portion of the small intestine, are responsible for producing GLP-1. Minutes after eating a meal, GLP-1 is released into the bloodstream; fat, carbs, and protein all seem to be potent GLP-1 secretion stimulants. 6 Following their release, GIP and GLP-1 both quickly lose their activation. The peptides are truncated by cutting off the N-terminal dipeptide end, which results in inactivation. The enzyme dipeptidyl peptidase 4 (DPP-4) performs this activity (22). The primary mechanism behind incretin action is the glucose-dependent stimulation of insulin secretion by both GIP and GLP-1. Hormone signalling is carried out by activating G-protein-coupled GIP and GLP-1 receptors. Although other pathways exist that are not reliant on protein kinase A, the complicated biochemical process underlying the insulinotropic effect of incretin hormones requires an increase in cAMP and the activation of protein kinase A. (23)

GLP-1 has been shown to promote islet neogenesis and differentiation as well as decrease b cell apoptosis in rats, in addition to stimulating insulin production (24). The modification of the expression of genes unique to islet b-cells, such as the homeodomain protein, is likely to be the mechanism behind these effects, which are linked to increased b-cell bulk (25). Glucagon secretion is influenced by the incretin hormones as well. Thus, it has been shown that GIP increases glucagon secretion, whereas GLP-1 decreases it (26).

Additionally, the incretin hormones affect the pancreas. Gastric emptying is prevented by both incretins. Through a central action, GLP-1 and GIP both stimulate lipogenesis and satiety, respectively. Hepatic vagal afferents are also stimulated by GLP-1 through portal GLP-1 receptors. Due to the fact that ganglionic blockade (16) and sensory deactivation (17) diminish GLP-1-stimulated insulin production in animals, this activity may help explain the hormone's insulinotropic effects. Finally, GLP-1 enhances endothelial and myocardial function (27).

Thus, GLP-1 has a wide range of effects (Figure 3), all of which have the potential to be helpful in the management of diabetes. As a result, the hormone has been investigated as a cutting-edge method of treating diabetes (28). Early 1990s studies revealed that intravenous treatment of GLP-1 lowered the insulin need for meal consumption in both type 1 and type 2 diabetes and that infusion of GLP-1 reduced the need for mealtime glucose monitoring in both types (29).

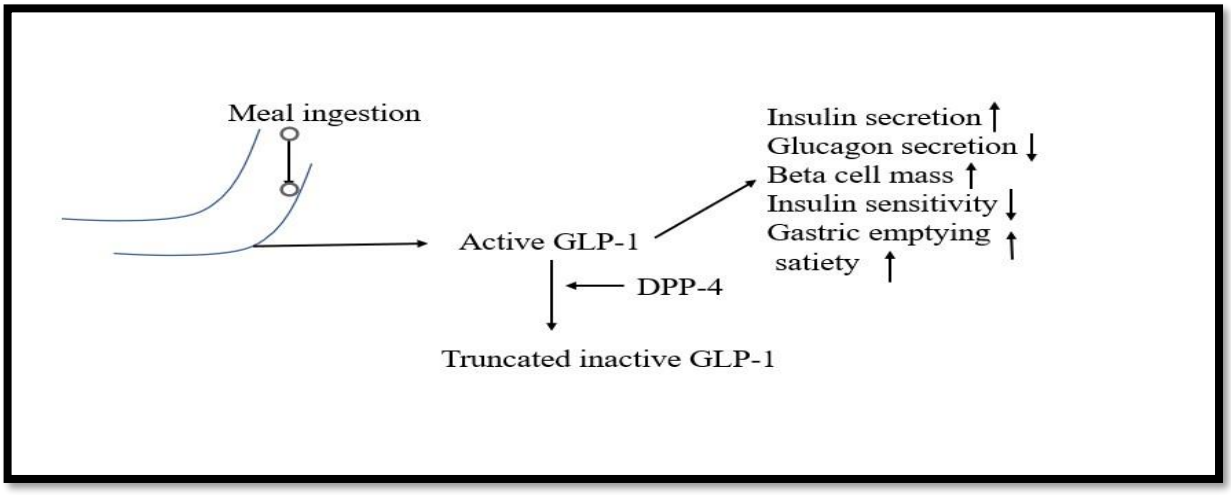

Figure 3. The effects of active GLP-1, its metabolism by dipeptidyl peptidase 4 (DPP-4), and the release of glucagon-like peptide 1 (GLP-1) after eating a meal.

Glucose levels in the blood are a sign of type-2 diabetes. A more recent 6-week study using continuous subcutaneous infusion of GLP-1 in subjects with type-2 diabetes showed the powerful antidiabetic action of GLP-1 (30). The rapid inactivation of GLP-1 by DPP4 has been a challenge in the development of GLP-1 as a novel treatment for type-2 diabetes because the truncated form of the peptide is largely inactive (31). Two approaches have been investigated and proven effective for solving this issue (32). Exenatide is an example of this method; it is a GLP-1 receptor agonist (also

known as a GLP-1 mimic) that is resistant to DPP-4 (33). The other strategy is to suppress the enzyme DPP-4, which delays GLP-1's inactivation and therefore strengthens and extends the incretin hormone's activity. These two tactics have been outlined in many recent studies (34).
While GLP-1 has generated significant attention as a potential treatment for diabetes, analogous research on GIP has proven unsatisfactory. This is mostly due to research showing that type-2 diabetes impairs GIP's insulinotropic function and that GIP increases rather than suppresses glucagon secretion.

7.2-DPP-4

Numerous organs express DPP-4, also known as DPP-IV, CD26, and EC 3.4.14.5, and it also circulates. DPP-4 cleaves oligopeptides after the second amino acid from the N-terminal end as one of its principal functions, acting preferentially if the second amino acid is alanine (as in GLP-1) or proline (35). Only 40% of the total GLP-1 in the circulation while fasting is active (and 60% after eating a meal), and the half-life of active GLP-1 is less than two minutes. This truncating impact of DPP-4 is quick and effective. This half-life is markedly extended by DPP-4 inhibition, which also raises the percentage of active GLP-1 in the overall pool of circulating GLP-1 (36).
Other bioactive peptides than incretin hormones have the potential to be DPP-4 substrates. DPP-4 may metabolise a number of chemokines, including substance P, neuropeptide Y, peptide YY, gastrin-releasing polypeptide, pituitary adenylate-cyclase-activating polypeptide, insulin-like growth factor-1, and others (37). This may suggest that DPP-4 regulates other homeostatic systems, such as blood pressure, neurogenic inflammation, and the immune system, in addition to glucose homeostasis. It is not yet known if these and other bioactive peptides are DPP-4 substrates in a physiological setting. DPP-4 may function as a receptor in addition to being an enzyme that truncates bioactive peptides to convey signals from extracellular to intracellular pathways (38). DPP-4 inhibitors do not seem to have an impact on this possible DPP-4 activity, which has not been well studied.

7.3-DPP-4 INHIBITION

DPP-4 is implicated in the control of glucose homeostasis because it truncates GLP-1, rendering it inactive. Findings showing that mice with a genetic deletion of DPP-4 had enhanced glucose tolerance after oral glucose treatment together with increased insulin production provide a good illustration of this (39). It was proposed in the 1990s that inhibiting DPP-4 might be a target for treating diabetes because of the possible antidiabetic impact of GLP-1 (40). Animal findings demonstrating that the DPP-4 inhibitor valine pyrrolide enhances active GLP-1 levels, increases insulin secretion, and improves glucose tolerance supported the reasoning for this hypothesis (41). It has been shown that in DPP-4 inhibitors (519 humans), DPP-4 inhibition raises the postprandial levels of active GLP-1 by almost three times, from (42) w5–6 p mol/L to w15–20 p mol/L.

7.4-DPP-4 Inhibitors

There are now five DPP-4 inhibitors on the market: vildagliptin, saxagliptin, linagliptin, alogliptin (available in both the United States and Europe), and sitagliptin (43). Only the Japanese and Korean markets have authorised four other gliptins, namely teneligliptin, anagliptin, Omari-gliptin, and trelagliptin.
The different gliptins vary in their pharmacologic and pharmacokinetic features while having the same mechanism of action, which may have therapeutic implications for certain patients (44; **Table 1**). However, their effectiveness in suppressing plasma DPP-4 activity and acting as antidiabetic drugs seems to be comparable (45). Potency, target selectivity, oral bioavailability, elimination half-life, binding to plasma proteins, metabolic pathways, formation of active metabolite(s), primary excretion routes, dosage modification for renal and liver insufficiency, and potential drug-drug interactions are the main differences between them (46)

Table 1. Comparing DPP-4 inhibitors that are presently on the marke

DRUG	DOSAGE FORMS	DOSAGE CHANGE IN RENAL DYSFUNCTION	DOSAGE CHANGE IN HEPATIC DYSFUNCTION	EXCRETION	DPP-4 INHIBITION	HALF LIFE (HOURS)	METABOLISM	AVAILABLE IN FIXED-DOSE COMBINATION
SITAGLIPTIN	25 mg							
	50 mg	Yes	No	Renal (~80% unchanged as parent	Max ~97%; >80% 24 h post-dose	8–24	Not appreciably metabolized	With metformin, With simvastatin
	100 mg							
SAXAGLIPTIN	2.5 mg	Yes	No	Renal (12–29% as parent, 21–52% as metabolite)	Max ~80%; ~70% 24 h post-dose	2–4 (parent) 3–7 (metabolite)	Hepatically metabolized to active metabolite (via P450 3A4/5)	With metformin, With dapagliflozin
	5 mg							
VILDAGLIPTIN	50 mg dose		Not recommended in severe dysfunction. Liver testing before administration	Renal (22% as parent, 55% as primary metabolite)	Max ~95%; >80% 12 h post-dose	1 1 ⁄2 – 41 ⁄2	Hydrolysed to inactive metabolite (P450 enzyme independent)	With metformin
	50 mg bid;							
	50 mg qD in Egfr<45 mi/min	yes						
ALOGLIPTIN	6.25 mg							
	12.5 mg	yes	no	Renal (>70% unchanged as parent)	Max ~90%; ~75% 24 h post-dose	12–21	Not appreciably metabolized	With metformin, With pioglitazone
	25 mg							
LINAGLIPTIN	5mg	no	no	Biliary (>70% unchanged as parent),6% via kidney	Max ~80%; ~70% 24 h post-dose	10-40 half life	Not appreciably metabolized	With metformin, With empagliflozin

Vildagliptin (LAF237; GalvusR, Novartis) and sitagliptin (MK-0431; Januvia R, Merck) have been studied in the greatest depth among the DPP-4 inhibitors that have been created **(Table 2).** (47). Both are competitive and reversible inhibitors of the enzyme, and they both exhibit sluggish, tight-binding inhibition characteristics. Both sitagliptin and vildagliptin are orally active and quickly absorbed; following oral ingestion, bioavailability is more than 80% and Cmax is seen in 1-2 hours (48). Although renal insufficiency raises the blood levels of sitagliptin, hepatic insufficiency does not seem to change the pharmacokinetics of the compounds (49).

Table 2. According to several public databases, dipeptidyl peptidase 4 (DPP-4) inhibitors are at various phases of clinical development**.**

Name	Company	Stage in development
Sitagliptin (JanuviaR)	Merck	Approved
Vildagliptin (GalvusR)	Novartis	Filed
Alogliptin	Takeda	Phase III
Saxagliptin	Bristol-Myers-Squibb	Phase III
PSN-9301	OSI Pharmaceuticals	Phase II
R1438	Roche	Phase II
TA-6666	Tanabe	Phase II
PHX1149	Phenomix	Phase II
GRC 8200	Glenmark Pharmaceutical	Phase II
SYR-619	Takeda	Phase I
TS-021	Taisho Pharmaceuticals	Phase I
SSR 162369	Sanofi-Aventis	Phase I
ALS 2-0426	Alantos Pharmaceutical	Phase I

8-DPP-IV inhibitor's therapeutic effects are mediated by glucagon-like peptide-1.

8.1- Inhibition of DDP-IV results in a modest rise in endogenous GLP-1

Whether the observed increases in plasma active GLP-1 concentrations are enough to account for the effects of DPP-IV inhibition on insulin production is the question at hand. Even if both therapies lead to comparable systemic increases in active GLP-1, we contend that it is difficult to compare the effects of DPP-IV inhibitors on peripheral venous concentrations of active GLP-1 with those of exogenous GLP-1 infusions. A rise in peripheral concentrations of the intact peptide following consumption of smaller meals is typically undetectable because GLP-1 is so extensively digested (50). Furthermore, it has been shown that a very considerable amount of the GLP-1 that exits the stomach has already been degraded into the inactive metabolite, even though almost all of the GLP-1 stored in the granules of the L-cells is still in its intact form (51). (52). **(Fig. 4).** Only around 10-15% of freshly produced GLP-1 enters the systemic circulation in the active state because an additional 40–50% of breakdown occurs in the liver (53). **(Fig. 4).** This degradation is caused by endothelial DPP-IV in the lamina propria capillaries, which may be totally stopped by DPP-IV inhibition (54). Furthermore, since portal blood is diluted as it reaches the systemic circulation, if DPP-IV inhibitors are shown to increase systemic venous concentrations of active GLP-1, it follows that they must have also raised portal venous plasma concentrations by a factor of 2-3. In accordance with this, there will also be an increase in the local concentration of GLP-1 in the lamina propria of the gastrointestinal mucosa (due to the fraction of the portal plasma flow that is derived from perfusion of the lamina propria). The impact of the DPP-IV inhibitors may be explained by these increases in active GLP-1 concentrations. It has been hypothesised that GLP-1 exerts a variety of activities either locally in the gut or in the hepatic portal bed as a result of the considerable degradation that takes place before it reaches the systemic circulation (55). GLP-1 may interact with afferent sensory nerve fibres emerging from the nodose ganglion after it is released, but before it penetrates the capillaries and comes into contact with endothelial DPP-IV, which sends impulses to the nucleus of the solitary tract (56) and onward to the hypothalamus **(Fig. 5).** This idea is supported by the recent discovery that nodose ganglion cells express the GLP-1 receptor. Additionally, it has been shown that intraportal GLP-1 injection enhances impulse activity in the vagal trunks (57), which might result in a pancreatic reflex. According to studies done on rats, ganglionic blockade lessens the insulin response that is induced by the intraportal infusion of glucose plus GLP-1 compared to when glucose is administered alone (58). Thus, the brain pathway may be more significant than the endocrine route for GLP-1-stimulated insulin production under physiological circumstances.

Because insulin levels are not boosted while receiving inhibitor medication, this condition should not be compared to infusion trials that do raise insulin levels (59). In order to achieve the same amount of insulin secretion at lower glucose levels, the insulinogenic index seems to be increased as a result of GLP-1's insulinotropic effects. The exogenous GLP-1 dosages necessary to have this effect have not yet been determined.

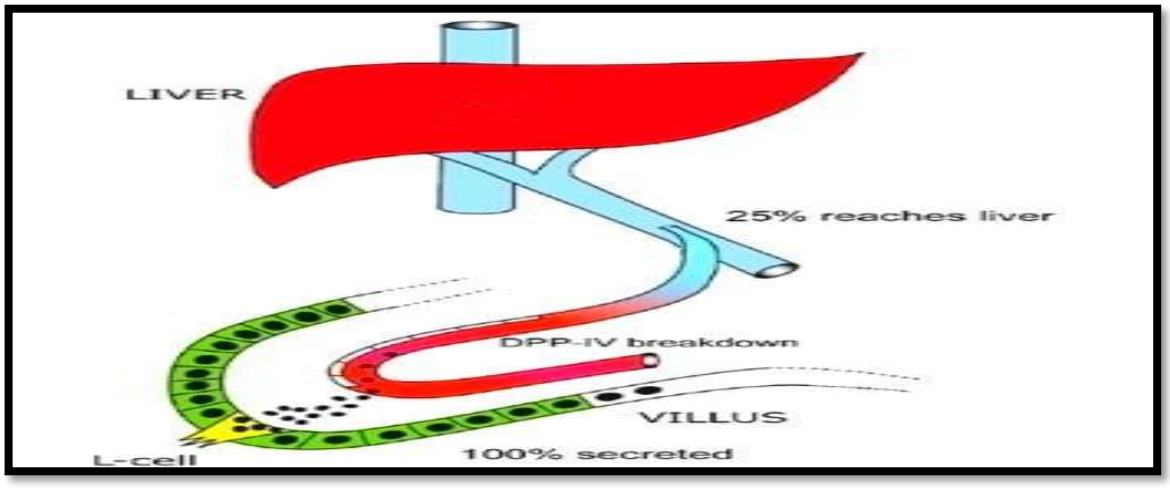

Fig. 4 Diagram of the endocrine system showing how GLP-1 works. Nutrition in the gastrointestinal lumen promotes GLP-1 secretion (a magnified intestinal villus with an open-type L-cell is shown in the lower left-hand corner). A capillary absorbs GLP-1 from the basal lamina into the lamina propria, where it is broken down by DPP-IV on the luminal side of the endothelial cells (white cells lining the capillary). As a result, only 25% of the produced GLP-1 enters the portal circulation. Only 10-15% of the substance reaches the systemic circulation, where it is transported to the pancreas and the brain through the endocrine route after another 40–50%–or more–of it is destroyed in the liver (perhaps even less will reach these regions because of the continued proteolytic activity of soluble DPP-IV present in plasma).

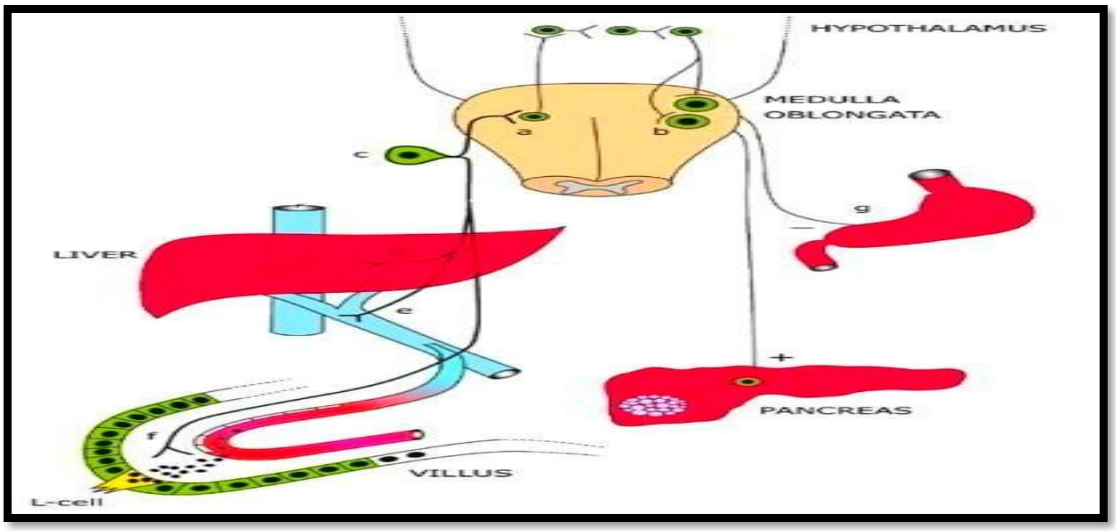

Fig. 5 Diagram of the neuronal system that GLP-1 uses to carry out its activities. A enlarged intestinal villus containing an open-type L-cell is shown in the bottom left-hand corner. Nutrients in the gut lumen induce GLP-1 production, and freshly produced GLP-1 diffuses over the basal lamina into the lamina propria. It may bind to and activate sensory afferent neurons (f) coming from the nodose ganglion (c) on the route to the capillary, which may then activate neurons in the solitary tract nucleus (a). In the hepatoportal area (e) or in the liver tissue, sensory neurons may engage the same neural pathway (d). In the hypothalamus, ascending fibres from the solitary tract neurons may cause reflexes, while descending impulses from vagal motor neurons (b) may cause stimulatory (h) or inhibitory (g) impulses to be sent to the pancreatic and gastrointestinal system, respectively.

8.2-Gastric emptying is not significantly affected by DPP-IV inhibitors

Although a comparable slowing has not been shown in experiments with DPP-IV inhibitors, it is stated that GLP-1 always inhibits stomach emptying at levels that impact blood glucose (60), although this conclusion is difficult to draw from the source cited for the latter claim (61). While identical glucose reduction was achieved with all doses of GLP-1 tested, stomach emptying was inhibited in a dose-dependent manner, contrary to the impression provided by the assertion that gastrointestinal deceleration follows the hypoglycaemic effects of GLP-1 (62). In other words, there was a rightward change in the dose-response relationship. Despite this, we concur that the available data points to a modest or non-existent impact of the inhibitors on stomach emptying. This may be connected to the finding that, despite DPP-IV inhibition for a year, there was no change in body weight (63). DPP inhibitors would not be anticipated to have a significant impact on gastric emptying, despite a rather pronounced effect on glucose levels, given that inhibitor treatment only doubles peripheral concentrations of intact GLP-1 and given the dose-response relationship for gastric emptying established by researchers (64). Exogenous GLP-1 affects the islets via the endocrine pathway, whereas endogenously produced GLP-1 is likely to influence gastric motility by interacting with afferent sensory neurons in the gastrointestinal tract. This may be the most significant distinction between DPP inhibitors and endogenous GLP-1 **(Figs. 4–5).** This interaction may occur before freshly

generated GLP-1 enters the gastrointestinal tract's capillaries or before it passes through the liver, when it is not fully or just partly destroyed by DPP-IV (65). Since there is little to no change in the local concentrations of intact GLP-1, it follows that DPP-IV inhibition may not significantly affect this activation, but larger concentrations of exogenous GLP-1 may reach and activate the same sensory neurons that endogenous GLP-1 does.

8.3-DPP-IV inhibitors do not produce nausea or vomiting, while GLP-1 and incretin mimics do
It is known that when the level of active GLP-1 in the blood exceeds 60 pmol/l, nausea will occur. Such amounts are never observed when DPP-IV inhibitors are employed, while they may be initially attained following subcutaneous injection of GLP-1 or GLP-1 mimics. The route for this adverse effect may include contact with receptors in the area postrema, a region of the blood-brain barrier with leaky fenestrated capillaries, which would be impacted by circulating levels of GLP-1 (66).

8.4-GLP-1 levels after meals decrease in response to DPP-IV suppression.
According to the argument, there is "limited possibility for plasma concentrations of endogenously released GLP-1 (67) to climb into the therapeutically relevant range" when L-cell secretion is feedback inhibited during inhibitor administration. There are a number of observations that may be made. First, despite lower L-cell secretion, all investigations have shown that the peripheral concentration of intact GLP-1 does rise (by a factor of 2) following inhibitor administration. Second, given the potential significance of the hepatoportal receptors, the inhibition of endothelial DPP-IV in the intestine's capillaries as well as the aforementioned dilution effect would result in higher amounts of active GLP-1 in the portal plasma. Third, we must keep in mind that the assessments of feedback inhibition published too far for both GLP-1 and GIP secretion are based on short-term investigations. DPP-IV inhibitors, on the other hand, have effects that take longer to manifest and may have a less noticeable impact on glucose levels in the beginning than they do in the latter stages (4–12 weeks). According to the theory that type 2 diabetes causes a reduction in GLP-1 production, likely as a result of the diabetic condition, active GLP-1 and GIP concentrations may alter throughout this time (68). With progressive changes in metabolism, incretin secretion or susceptibility to their effects could increase. For instance, it has been shown that high blood sugar levels downregulate the GIP receptor (69), while the responsiveness to GIP has been seen to improve after antihyperglycemic treatment with glyburide to lower fasting glucose levels in diabetic patients (70).

8.5-The effects of DPP-IV inhibition on glucose homeostasis are delayed.
The effects of the inhibitors take time to manifest, as previously stated by our opponents, but the benefits of GLP-1 are rapid. Although the exact cause of this is uncertain, it is likely that it is connected to a gradual increase in secretion and maybe an improved action of the incretin hormones, whose sensitivity is significantly decreased in uncontrolled diabetes (71).
We come to the conclusion that every objection raised by our opponents may really be refuted in favour of the theory that the primary effects of DPP-IV inhibitors are mediated via GLP-1. The suppression of glucagon production may be one of the most significant therapeutic effects of GLP-1, as also seems to be the case with the DPP-IV inhibitors—once again, a remarkable similarity—and we would like to emphasise that this debate may have concentrated too much on insulin secretion. Pancreatic neuropeptides have been proposed as potential substitute mediators by our opponents, and this is still a possibility. Uncertainty surrounds the significance of pancreatic innervation for postprandial insulin secretion in people. We draw the conclusion that the data so far supports the idea that protecting GLP-1 plays a significant role in the effects of DPP-IV inhibition (72).

9-Inhibitors of DPP4: Clinical safety
In several meta-analyses, the DPP4 inhibitors' effectiveness and safety have been documented. Sitagliptin and Vildagliptin were shown to be extremely effective for controlling blood sugar and to be more likely to lower glycosylated haemoglobin than placebo in a comprehensive evaluation of 29 trials published between 2004 and 2007. (73). Patients on DPP4 inhibitor treatment generally had a

low incidence of adverse events, such as infections and gastrointestinal issues including nausea, diarrhoea, and vomiting (74). Compared to non-incretin-based hypoglycemic medications, urinary tract infections were the most frequent adverse event for all DPP4 inhibitors. In later investigations, the incidence of infections, particularly those of the upper respiratory tract and the urinary tract, was not significantly different between individuals receiving DPP4 inhibitors versus placebo or standard diabetic therapy.

Acute pancreatitis is the most common significant adverse event linked to the use of DPP4 inhibitors, notwithstanding its rarity. When compared to other treatments, sitagliptin usage elevated the chance ratio for pancreatitis by six times, according to a study of adverse event data submitted to the FDA during a nine-year period (75). When compared to individuals on other type-2 diabetes drugs, the incidence of pancreatitis remained unaffected in patients receiving Sitagliptin (76), according to a comprehensive retrospective analysis that examined pharmaceutical claims data from 786,656 patients. DPP4 inhibitor usage is associated with a slightly increased risk of developing acute pancreatitis, according to recent meta-analyses of the DPP4 inhibitors Sitagliptin, Alogliptin, Linagliptin, Saxagliptin, and Vildagliptin (77). A minor but elevated incidence of pancreatitis was also seen in the Linagliptin-taking individuals in the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) study (78). However, there was no elevated incidence of pancreatitis in the Linagliptin group, according to the Cardiovascular Outcome Trial of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA) study (79). A TNF-, IL-1, IL-6, and IL-8-pro-inflammatory immune response, driven by neutrophils and macrophages, is a hallmark of acute pancreatitis (80). (81). Although the precise pathways linking the use of DPP4 inhibitors with pancreatitis remain unclear, their impacts on innate immunity may provide new information on their pharmacological properties.

10- Innate immunity and dipeptidyl peptidases

DPP4 inhibitors may affect innate immune responses, according to emerging research, which may have clinical repercussions. Although DPP4's function in adaptive immunity has previously been discussed, it is becoming more-clear that DPP4 inhibitors may change several aspects of innate immunity, including responses from vascular endothelial cells, neutrophils, and monocyte/macrophages **(Fig. 6).** The wide variety of DPP4 substrates and their overlapping functions in innate immunity imply that DPP4 inhibition may have an effect on several pathways **(Table 3).**

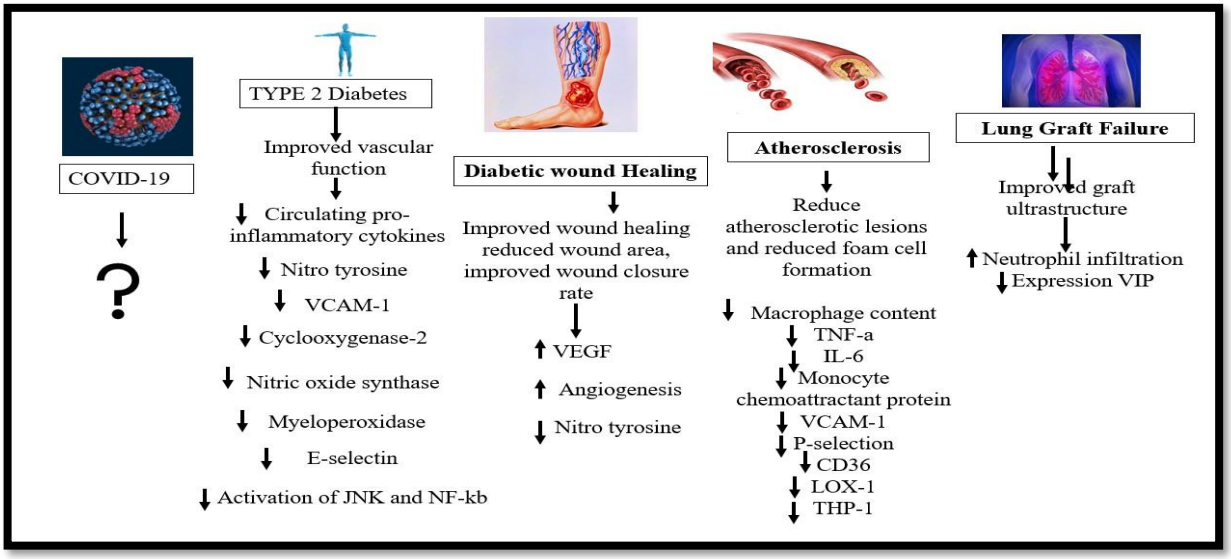

Fig. 6. An overview of the major medical issues covered in this review, together with the physiological and molecular impacts of DPP4 inhibition. Reduced expression is denoted by, whereas enhanced expression is denoted by.

10.1-blood vessel endothelium

The vascular system's endothelial cells are crucial for preserving blood flow and vessel tonicity as well as playing significant roles in controlling the innate immune response (82). Endothelial cells that have been activated release a variety of cytokines, chemokines, and the cellular adhesion molecules intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) that are necessary for the attraction, activation, binding, and tethering of polymorphonuclear leukocytes, including monocytes and neutrophils (83). Endothelial dysfunction, also known as chronic and persistent endothelial activation, has been linked to the pathophysiology of inflammatory diseases such inflammatory bowel disease and rheumatoid arthritis as well as cardiovascular disease (85).

Independent of their anti-hyperglycemic activity, DPP4 inhibitors have been linked to significant improvements in vascular endothelial function in type-2 diabetes. After six months of Sitagliptin (50 mg/day) medication, compared to conventional therapy, endothelial function was dramatically improved in individuals with type-2 diabetes and pre-existing coronary artery disease (86). a decrease in blood levels of pro-inflammatory cytokines and the indicator of oxidative stress, nitro tyrosine, among Type-2 diabetics using either Sitagliptin or Vildagliptin, according to prospective, randomised open-label research (87). Vildagliptin produced better results, according to the authors, indicating that glycaemic management and inhibitor kinetics were involved in the immunomodulatory effects. The likelihood of a non-glycaemic impact of DPP4 inhibitors in controlling endothelium-mediated innate immunity (88) was not entirely disregarded by the authors.

10.2-Neutrophils

When infections invade, neutrophils, which are highly specialised anti-microbial immune cells, are the first to react (89). To eliminate invasive infections, neutrophils use a variety of cellular and non-cellular methods, including as phagocytosis and the release of powerful antibiotics, proteases, and reactive species (90). Additionally, by secreting a variety of cytokines and peroxidases, neutrophils play a crucial role in triggering the secondary immune response by attracting and stimulating macrophages, dendritic cells, and lymphocytes to the site of inflammation (91). DPP4 inhibitors may be able to modify some elements of neutrophil recruitment and activity, according to pre-clinical and in vitro investigations.

In order to avoid infection by harmful organisms, neutrophil recruitment and activation is a crucial step in the normal cascade of events that characterises wound healing (92). Diabetes patients have a decreased leucocyte function, which might affect how well neutrophils migrate to the wound (93). However, the presence of neutrophils at the wound site in chronic, non-healing wounds, such as those observed in diabetics, may increase tissue damage by releasing reactive oxygen species, anti-microbial peptides, and proteases (94). A prospective, randomised open label experiment was conducted to examine Vildagliptin's impact on diabetic chronic ulcer wound healing. When compared to patients receiving standard therapy, Vildagliptin treatment for three months substantially reduced total wound area, wound-related problems, and improved wound closure rates (95). The Vildagliptin group showed enhanced angiogenesis and vascular endothelial growth factor expression, according to the scientists (96). Leukocyte infiltration was not explicitly measured, however Vildagliptin-treated individuals showed a reduction in nitro tyrosine, a substance linked to active neutrophils. Researchers found that animals treated with Linagliptin had lower levels of infiltrating neutrophils in a mouse model of diabetic wound healing. The authors hypothesised that Linagliptin may indirectly affect neutrophil recruitment through COX-2 and MIP-2 (97). This pre-clinical evidence backs up the findings from human studies and indicates that DPP4 inhibition may provide protection via a potential COX-2 and MIP-2 mediated mechanism.

Table 3. Candidate DPP4 substrates known to have a role in innate immune reactions.

S.NO	**Substrate**	**N-terminal sequence**	**Reported Roles in Innate Immunity**	**Biological Effect of DPP4 cleavage**
1	Eotaxin (CCL11)	Gly-Pro-Ala	Eosinophil and basophil migration	Reduced chemotactic activity
2	Erythropoietin	Ala-Pro-Pro	Inhibits production of macrophage derived inflammatory cytokines; enhances macrophage phagocytic activity	Inactivation
3	Gastrin-releasing peptide (GRP)	Val-Pro-Leu	Induces neutrophil migration	Inactivation
4	Glucagon like peptide 1 (GLP-1)	His-Ala-Glu	Induces macrophage polarization	Inactivation
5	Granulocyte-Colony Stimulating Factor (G-CSF	Glu-Ala-Thr	Stimulates neutrophil proliferation & differentiation	Inactivation
6	Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF)	Ala-Pro-Ala	Recruitment of neutrophils & monocytes; stimulates macrophage activity	Inactivation
7	HMGB1	Gly-Lys-Gly	Stimulates expression of cell adhesion molecules; upregulates proinflammatory cytokine production	Inactivation
8	IP10 (CXCL10)	Val-Pro-Leu	Chemoattractant for monocytes/macrophages & NK cells; stimulates NK cell degranulation	Reduced chemotactic potential
9	ITAC (CXCL11)	Phe-Pro-Ala	Chemoattractant for monocytes/macrophages & NK cells	Reduced chemotactic potential
10	IL-3	Ala-Pro-Me	Monocyte activation & differentiation	Inactivation
11	Macrophage-derived chemokine (MDC, CCL22)	Gly-Pro-Tyr	Recruitment of dendritic cells, NK & Th2 cells	Reduced chemotactic potential
12	Monokine induced by IFN-γ (Mig, CXCL9)	Tyr-Pro-Val	Recruitment of T-cells,	Reduced chemotactic potential
13	Neuropeptide-Y (NPY)	Tyr-Pro-Ser	Stimulates secretion of pro-inflammatory cytokines by macrophages; stimulates phagocytic activity	Altered receptor specificity
14	RANTES (CCL5)	Ser-Pro-Tyr	Recruitment of macrophages and NK cells	Altered receptor specificity
5	Stromal-cell derived factor (SDF-1, CXCL12)	Lys-Pro-Val	Monocyte chemoattractant	Reduced chemotactic potential
16	Pituitary adenylate-cyclase-activating polypeptide (PACAP)	His-Ser-Asp	Inhibit macrophage chemotaxis, phagocytosis & ROS production; inhibits pro-inflammatory cytokine production by macrophages	Inactivation
17	Substance P	Arg-Pro-Lys	Stimulate neutrophil & macrophage phagocytic activity; stimulates proinflammatory cytokine production in mast cells; enhances NK cell cytotoxicity	Inactivation
18	Vasoactive Intestinal Peptide (VIP)	His-Ser-Asp	Inhibit macrophage chemotaxis, phagocytosis & ROS production; inhibits pro-inflammatory cytokine production by macrophages	Inactivation

11-pharmaceuticals and pharmaceutical dynamics

Since dipeptidyl pepitidase-4 was initially discovered in 1966, a lot has been learned about its kinetics and substrate selectivity (98). Several DPP-4 inhibitors were developed using this knowledge, including vildagliptin and saxagliptin, which were discovered through drug discovery programmes based on structure-activity profiling. This information served as the foundation for the DPP-4 inhibitor idea (99). The DPP-4 crystal structure was published around the turn of the century, and new, closely related DPP-4 enzyme family members, including DPP-8 and DPP-9, were also found (100). Preclinical toxicities have been reported with several prototype DPP-4 inhibitors, and it was

subsequently hypothesised that these toxicities could have been caused by off-target inhibition (101) of DPP-8 and/or -9. Further optimization led to compounds with improved selectivity for DPP-4 (alogliptin, anagliptin, Evo gliptin, gemigliptin, linagliptin, Omari gliptin, sitagliptin, and teneligliptin (102)); however, despite differences in enzyme selectivity between DPP-4 inhibitors being evident in in vitro studies **(Table 4),** there is currently no proof of side effects associated with off-target inhibition

Drug	QPP/ DPP II	PEP	FAP α	DPP-8	DPP-9
Alogliptin	>14 000	>14 000	>14 000	>14 000	>14 000
Anagliptin	n.r.	n.r.	n.r.	>16 000	>15 000
Evogliptin	>20 000	n.r.	>20 000	6 000	6 000
Gemigliptin	>25 000	n.r.	n.r.	10 560	2 940
Linagliptin	>100 000	>100 000	89	40 000	>10 000
Omarigliptin	>41 000	>41 000	>41 000	>41 000	>41 000
Saxagliptin	>50 000	n.r.	>4 000	390	77
Sitagliptin	>5 550	>5 550	>5 550	>2 660	>5 550
Teneligliptin	n.r.	n.r.	>11 000	700	1 500
Vildagliptin	>100 000	60 000	285	270	32

Table 4Dipeptidyl peptidase (DPP)-4 inhibitors' in vitro selectivity (expressed as fold selectivity relative to selectivity for DPP-4)

12-Advantages of DPP4i

DPP4i all gain from being widely accessible and well-tolerated anti-hyperglycaemic medicines that may be used orally (105). Additionally, they are simple to use, don't need dosage titration, and may be used throughout the day, regardless of mealtimes. Because of their dual insulinotropic and glucagon static actions in their mode of action, they work well in combination with other anti-diabetic medications to increase HbA1c-lowering effectiveness **(Table 5)**. In this regard, the individual DPP4i have a low propensity for drug-drug interactions, meaning they can be used with any other medications without the need for dosage adjustment. However, due to its route of metabolism, the effectiveness of saxagliptin may be decreased if used in conjunction with strong inducers of P450 3A4, such as rifampicin. Similar to DPP4i, other drugs do not often need dosage adjustments; however, to reduce the risk of hypoglycaemia brought on by sulfonylureas and insulin, it is advised to reduce concurrent sulfonylurea or insulin doses (106). A second explanation for the unique efficacy of the metformin and DPP4i combo is the revelation that metformin may promote GLP1 production and that this effect adds to metformin's action (107). Additionally, because to DPP4i's dual effects on -cells and -cells, they work effectively in conjunction with sodium-glucose transporter 2 inhibitors' pancreatic islet-independent activity (SGLT2i). Additionally, when DPP4i are used with insulin secretagogues or insulin itself, the reduction in hepatic glucose production caused by DPP4i due to the suppression of glucagon secretion provides a complementary effect **(Table 5)**. This also means that beneficial effects on glycaemic control can still be obtained, even if -cell function is diminished (108).

Table 5. | Anti-diabetic drug primary effects, highlighting complementary modes of action

Anti-diabetic agents	Improved insulin levels	Improved insulin resistance	Reduced hepatic glucose overproduction	Reduced glucose absorption or reabsorption
Metformin	NA	Improves hepatic and muscle insulin sensitivity	Decreases gluconeogenesis	NA
Sulfonylureas	increase insulin exocytosis	NA	NA	NA
Glinides	increase insulin exocytosis	NA	NA	NA
Thiazolidinediones	NA	Improve insulin sensitivity in adipose	NA	NA

		tissue, muscle and liver		
DPP4i	Increase insulin biosynthesis and secretion (glucose-dependent). Indirect effect via enhancing incretin levels to improve β-cell function	NA	Decreases glycogenolysis and gluconeogenesis. Indirect effect via enhancement of GLP1 levels resulting in suppression of glucagon (glucose-dependent)	NA
SGLT2i	NA	NA	NA	Reduce renal reabsorption
α-glucosidase inhibitors	NA	NA	NA	Reduce intestinal uptake
GLP1 agonists	Improve β-cell function by increasing insulin biosynthesis and secretion (glucose-dependent)	NA	Decrease glycogenolysis and gluconeogenesis. Indirect effect via suppression of glucagon (glucose-dependent)	NA
Insulin	Exogenous administration	NA	NA	NA

13- REASONS WHY DPP-4 INHIBITORS ARE USED

13.1-changes to GLP-1

When administered to diabetes patients and healthy volunteers, DPP-4 inhibitors induce circulation levels of active GLP-1 to more than double those in placebo-treated participants. In both healthy persons and diabetics, only one-third to half of the circulating GLP-1 during the post-prandial phase is in an active state; the remainder is made up of inactive fragments. DPP-4 inhibition only slightly raises GLP-1 plasma levels when the active fraction, not the total fraction, is elevated, favouring its physiological activity and preventing adverse effects that may be brought on by high levels (109).

13.2-Effects on A- and B-cell function

Pancreatic A- and B-cell dysfunction together with an imbalance between glucagon and insulin production characterises type 2 diabetes. DPP-4 inhibitors make B-cells more sensitive to glycaemic levels. This was shown, for example, in a double-blind trial on 9 newly diagnosed diabetics who received vildagliptin 100 mg twice daily instead of 11 individuals who received a placebo for 4 weeks (110). Patients had conventional meals at the conclusion of the fourth week, and their glycemia, insulinemia, and C-peptide levels were assessed. The results were translated into a mathematical model, which was used to derive certain B-cell functioning metrics and correlate insulin secretion rates with glycemia. Vildagliptin was shown to substantially and consistently enhance the rate of insulin secretion at different glucose concentrations. The same research also showed that the elevated glucagonemia brought on by the meal is inhibited by vildagliptin. The stronger the glucose tolerance, the more the glucagonemia is reduced. Vildagliptin thereby compensates for the altered secretion of both glucagon and insulin, which are the two primary complications of Type 2 diabetes. It may also increase insulin sensitivity, albeit this may just be a side effect of the better glycaemic management (111).

14.Preclinical research

14.1-Animal studies

DPP4 inhibitor therapy increases glucose tolerance in obese Zucker rats (both diabetic and non-diabetic), ob/ob mice, Sprague-Dawley insulin-resistant mice given a high-fat diet, and obese and insulin-resistant Cynomolgus monkeys, according to a number of studies (112). DPP-4 inhibitors have also been shown to be effective against diabetes in mice in more recent research, highlighting their significance in boosting and maintaining B-cell activity over time (113).

15-clinical research

A number of DPP-4 inhibitors are now being investigated in stages 2 or 3, both alone and in combination with other anti-diabetic medications.

Early research on people with Type 2 diabetes and healthy volunteers shown that a single dosage of a DPP-4 inhibitor might lessen glycaemic excursions. Later, tests on diabetes patients in the clinic revealed that this therapy might enhance metabolic control by raising insulin secretion and lowering glucagon secretion.

A phase-2, multicentre, randomised, double-blind clinical investigation involves treating 37 Type 2 diabetes participants vildagliptin (100 mg/day) for 4 weeks (114). Vildagliptin effectively suppressed the activity of DPP-4 for 12 hours in these individuals who had not previously received anti-diabetic medication. Significant increases in GLP-1 concentrations were seen during fasting and at peaks 30 minutes after meals, simulating GLP-1 levels in healthy non-diabetic people. Despite the short research duration, levels of glycosylated haemoglobin (HbA1c) were considerably lower compared to the control group. There were no changes in either the lipid or weight profiles. There were extremely few negative side effects, and no hypoglycaemic incidents were reported. This research shows that vildagliptin is very well tolerated and may enhance metabolic control in diabetics who were previously treated with diet alone (115).

Another research looked at the effectiveness and tolerability of different vildagliptin doses in Type 2 diabetes individuals for 12 weeks (116). Four groups got vildagliptin treatment (25, 50, or 100 mg twice day), whereas the control group received a placebo. The results demonstrated that, compared to the placebo, vildagliptin dosages of 50 or 100 mg substantially lowered HbA1c levels after 12 weeks. Vildagliptin was well tolerated at all experimental doses and had no effect on lipid profiles or body weight. There were 17 hypoglycaemic incidents in the 297 individuals evaluated, equally divided throughout the groups, including the placebo group (117).

Another 12-week experiment compared the effectiveness and safety of vildagliptin 25 mg twice day with placebo in 28 participants to 72 patients (118). The baseline means HbA1c in this sample, which had not previously received treatment for diabetes, was 8%. Vildagliptin caused a considerable decrease in HbA1c and glycemia levels. Patients using vildagliptin had adverse events 15.7 percent more often than those taking a placebo (10.7 percent more frequently). Cases of mild hypoglycaemia were the most frequent adverse effects (in 10 percent of patients). Thus, these trials show that vildagliptin is highly well tolerated and may enhance metabolic control in Type 2 diabetics when used in monotherapy (119).

15.1-combined treatment

56 individuals with type 2 diabetes were included in a 12-week, randomised, double-blind experiment and given 50 mg/day of vildagliptin. In addition to a consistent dosage of 1500–3000 mg/day of metformin, 51 patients also got a placebo. HbA1c and fasting glycemia mean levels decreased in the treated group. Despite the fact that insulin levels were constant compared to baseline, the vildagliptin group's peak glycaemic post-prandial insulin response rose, which was explained by the B-cells' improved response to the post-prandial glycaemic peak. In an open-label extension of the experiment, patients who had completed the first 12 weeks of therapy were then requested to continue for an additional 40 weeks. Sixty-six percent of the initial group (71 patients, 42 of whom were given vildagliptin and 29 were given a placebo) completed the extended experiment. Following a year of therapy, the HbA1c values in the vildagliptin group dramatically decreased and were 1.1 percent below the mean compared to controls. Fasting glycemia decreased considerably in the vildagliptin group compared to the placebo group. 42 percent of patients on vildagliptin and metformin, compared to 11 percent of patients taking a placebo and metformin, achieved HbA1c values of less than 7 percent. Additionally, the levels of glucagon and post-prandial insulin secretion were not changed in the placebo group, while they were much lower in the research group. The suppression of glucagon secretion and the insulinotropic action both helped this medication provide effective glycaemic control outcomes (120).

Other research has shown the effectiveness of 100 mg/day of vildagliptin together with 1500 mg/day of metformin in lowering HbA1c levels, as well as in conjunction with 30 mg/day of pioglitazon in achieving the therapeutic aim of HbA1c..

15.3-Phase 3

studies One research examined the use of metformin against vildagliptin in the treatment of 780 individuals. HbA1c levels were dramatically lowered with both medications after a year of treatment. Compared to metformin, vildagliptin had improved tolerability (e.g., the frequency of diarrhoea was 4 times higher in the metformin group). There was no weight gain caused by any medicine (121).
In a separate research, 296 individuals with advanced Type 2 diabetes who were not properly managed with insulin were compared to vildagliptin and a placebo. Compared to the placebo, Vildagliptin 100 mg/day dramatically decreased HbA1c levels and insulin demand (122).

15.4-negative incidents

Vildagliptin is very well tolerated by Type 2 diabetic patients. It's critical to keep in mind that vildagliptin's effectiveness is dependent on blood sugar levels and that, as a result, hypoglycaemic effects are seldom reported (123). GLP-1 has an insulinotropic effect, however it only stimulates the production of insulin when blood glucose levels are over 90 mg/dl. This sets DPP-4 inhibitors apart from sulfonylurea, which secretes insulin regardless of blood sugar levels (124).
In terms of body weight, DPP-4 inhibitors do not cause weight fluctuations, which is another significant benefit over other popular treatment medications like thiazolidinediones, sulfonylureas, and insulin. The number of adverse events seen in clinical research is generally comparable in the treated and placebo groups, with flu-like symptoms, light-headedness, and headache being the most prevalent occurrences (125).

16-With a variety of side effects, these anti-diabetic medications assist people with DM in maintaining their blood glucose levels (Table 6).

Table 6. Currently available hypoglycaemic medications and their negative effects**.**

Class	Name	Mechanism	Side effect
Sulfonylurea	Glimepiride, Glyburide, Gliclazide	Insulin secretion	Hypoglycaemia, obesity
Meglitinides agonist	Repaglinide, Nateglinide	Insulin secretion	Hypoglycaemia, obesity
Thiazolidinedione	Pioglitazone, Rosiglitazone, Lobeglitazone	Increase insulin sensitivity	Obesity, edema
DPP-4 inhibitors	Sitagliptin, Vildagliptin, Saxagliptin	Increase insulin sensitivity	Indigestion, rash
Biguanide	Metformin	Reduce gluconeogenesis	Lactoacidosis, indigestion
Amylase/ glucosidase inhibitors	Acarbose, Miglitol, Voglibose	Inhibit starch digestion	Diarrhoea, flatulence
Sodium/glucose transporter inhibitors	Dapagliflozin, Canagliflozin, Empagliflozin	Reduce urine glucose reabsorption	Urinary and genital tract infection

17-A description of DPP-4 and its biological role

17.1-Two variations of DPP-4

The 88 kDa serine protease DPP-4 has a region comprising cytoplasmic (amino acids 1-6), transmembrane (amino acids 7–28), and extracellular (amino acids 29–766) amino acids, along with the primary catalytic domain (126). The body has two DPP-4 isoforms: soluble DPP-4 (sDPP-4), which lacks the cytoplasmic and transmembrane sections, and membrane-bound DPP-4 (mDPP-4), which is made up of the full-length DPP-4 peptide. Both types are capable of a range of biological processes that control physiology and disease (127).

17.2-The biological purpose of the soluble form DPP-4

Lymphocytes release sDPP-4, which circulates in the blood and has a high quantity in the kidney (128). It has been shown that sDPP-4 enhances skeletal muscle activity, immune cell activation, chemotaxis, and homeostasis in a number of ways. Skeletal muscle cells may respond by secreting sDPP-4 into the blood in response to intense physical activity or protein hydrolysate consumption (129). sDPP-4 secretion may decrease neuropeptide Y (NPY)-induced vasoconstriction and consequently increase skeletal muscle's arteriolar diameter, which offers a physiological explanation for the improvement in training effectiveness brought on by sDPP4. In addition to increasing skeletal muscle arteriolar diameter, secreted sDPP-4 functions as a myokine that triggers inflammation in blood vessel smooth muscles by activating the protease-activated (130) receptor 2 (PAR2)/ERK/NF-B signalling pathway, boosting the release of pro-inflammatory cytokines, and ultimately promoting smooth muscle cell proliferation (131). However, the body does not always benefit from smooth muscle inflammation caused by sDPP-4. For instance, it has been suggested that sDPP-4 may activate the same signalling pathway as smooth muscle inflammation to generate microvascular endothelial dysfunction, which is the root cause of chronic kidney disease in older people (132). As a result, Dubé et al. demonstrated how a DPP-4 inhibitor may reduce cardiovascular inflammation during HIV therapy, which lowers the risk of cardiovascular morbidity (133). Through co-stimulation with T-cell receptor (TCR) signalling and the Toll-like receptor, which is activated neither by its enzymatic activity nor by adenosine deaminase binding, sDPP-4 may promote T-cell proliferation in the context of T-cell activation (134). On the other side, via caveolin-1/ERK/NF-B/cFos signalling, which is implicated in monocyte proliferation, sDPP-4 may increase the production of IL-6 and TNF- in monocytes. It is significant that this study demonstrated a relationship between Tat, the HIV-1 transcription regulator, and DPP-4 (HIV-1-Tat). Further research is required to fully understand the impact on DPP-4/HIV-1-Tat in viral infection and proliferation. The breakdown of chemokines is connected to sDPP-4's function in regulating chemotaxis (135). Both colony-stimulating factors (CSFs), a substrate of both sDPP-4 and mDPP4, and stromal cell-derived factor 1 (SDF-1/CXCL12) are known to recruit hematopoietic stem cells (136).

17.3-Function of membrane-bound DPP-4 in biology

Surprisingly, the kidney, gastrointestinal tract, T lymphocytes, and reproductive organs are the primary locations of mDPP-4 (137). The modulation of immune response and blood vessel function are two examples of mDPP-4's biological functions. A T-cell co-stimulator of T-cell receptors responding to antigen-presenting cells is mDPP4, also known as CD26. As a result, mDPP-4 is now thought to be a promising target in the treatment of autoimmune illnesses and transplantation. a fascinating investigation on the effects of mDPP-4 inhibition in the first trimester that may help with the management of recurrent implantation failure (126). Graft-versus-host disease (GVHD) is a frequent complication in hematopoietic stem cell transplantation and has a significant impact on the survival probability following transplant. The author established a link between Th17 cells and GVHD and demonstrated that Th17 cells may be controlled by mDPP-4 inhibition, indicating that existing DPP-4 inhibitors can help slow the development of GVHD (138). mDPP-4's influence on immunological control is linked to autoimmune disorders and hypersensitivity. Patients with Hashimoto's thyroiditis had much lower levels of mDPP-4 expression in their CD8+ T cells than healthy individuals, which is likely due to the disease's development. In contrast, mDPP-4 levels are about 11 times greater in psoriatic skin than in normal skin, indicating that mDPP-4 is involved in the onset of psoriasis. Through encouraging T-cell activation, mDPP-4 contributes to the improvement of asthma. These studies have conclusively shown that mDPP-4 has a beneficial function in immune modulation. mDPP-4 controls blood vessel function by interacting with both endothelial and epithelial cells. The involvement of mDPP-4 in endothelium usually entails endothelial migration, angiogenesis, and proliferation under hypoxic conditions, which may be detected in the development of endometriosis in addition to the endothelial inflammation induced by sDPP-4. DPP-4 inhibitors, as the authors have shown, may lessen pulmonary arterial remodelling and, ultimately, postpone the

onset of pulmonary hypertension. By preventing mDPP-4/SDF-1-related angiogenesis, mDPP-4 inhibition may restore diastolic left ventricular dysfunction in the control of cardiovascular function (139). The involvement of mDPP-4 in the epithelial-mesenchymal transition (EMT) for epithelial cells raises the possibility that mDDP-4 has a role in accelerating the growth of cancer. In fact, by blocking the CXCL12/CXCR4/mTOR pathway, DPP4 may decrease the spread of breast cancer. DPP-4 inhibitors, however, have the opposite effect in non-small cell lung cancer, which inhibits cancer cell proliferation via macrophage-mediated activation of natural killer (NK) cells (140). These studies show that DPP-4 inhibition (sDPP-4 or mDPP-4) may have unanticipated side effects and have provided detailed explanations of the biological roles of mDPP-4 throughout the body.

17.4- Using DPP-4 to treat diabetes

DPP-4's endocrinological effect is more pronounced in the regulation of blood sugar. Due to with longer incretin half-lives in the blood, particularly in type 2 DM, DPP-4 inhibition is a common (141) approach for treating diabetes. Additionally, two 4-year clinical studies in which sitagliptin was used to treat slowly progressing type 1 DM (SPTIDDM) and latent autoimmune diabetes in adults have shown that sitagliptin may sustain pancreatic cell function and therefore stabilise insulin production (LADA). DPP-4 levels may be used as a biomarker in addition to clinical therapy. For example, high blood sDPP-4 levels may be linked to increased glycation end products, which in turn cause endothelial cell damage and increase the likelihood of diabetic nephropathy. Additionally, high blood sDPP-4 levels are associated with hyperglycemia, which is a sign of poor glycaemic control and accelerated disease progression, as well as a poorer therapeutic response to DPP-4 inhibitors (142). The aforementioned details highlight the importance of DPP-4 surveillance and inhibition in the management of diabetes. The following presents the procedure for screening DPP-4 inhibitors as well as the most current known natural DPP-4 inhibitors.

18-Techniques for evaluating potential DPP-4 inhibitors

18.1-DPP-4 inhibitors are being tested in simulation.

Drug discovery and development have smoothly incorporated virtual screening, and it heavily depends on compound libraries, particularly their structural diversity (143). For instance, DDP-4 inhibitors were searched for in microalgal metabolites. Natural compound libraries are superior screening resources because they often include more structurally varied compounds than synthetic chemical libraries do (144). Thus, as shown in **Table 7**, multiple investigations have used different natural chemical libraries to discover new DDP-4 inhibitors.

Table 7. Various research has employed natural compound libraries.

Natural compound library
Traditional Chinese Medicine Database (TCM Database Taiwan)
Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target database (NPACT)
Natural Products subset of the ZINC database
The Binding Database (Binding DB
Antidiabetic natural compounds database (ADNCD
Phenol-explorer
In-house natural products database (NPD)
The NuBBE Database (NuBBEDB)

18.2-Direct evaluation of substances against DPP-4

For screening DPP-4 inhibitors for direct testing, there are four different assay methods: direct enzymatic assay, in vitro cell assay, ex vivo assay, and in vivo animal tests. In the direct enzymatic assay, DPP-4 and the examined substances are combined with certain substrate peptides, such glypro-

p-nitroanilide. The quantity of the chemical p-nitroanilide produced from peptides is measured by optical absorption at 405 nm in the noninhibition condition (145). This technique may be used to assess the inhibition pattern using estimated Ki values and is quick to analyse. Direct enzymatic assay's little alterations, however, cannot be directly correlated with cells' and animals' true bioactivity. Ex vivo assays are able to mimic biological interactions that occur within the body, but they need fresh serum or tissue samples as the source of DPP-4 (146). In addition, earlier research suggested that mucosal DPP-4 suppression could be connected to the formation of coeliac disease, an autoimmune condition brought on by the immune system's reaction to gluten. Modern DPP4 activity assays, however, call for homogenising the whole intestinal sample, which may result in mucosal DPP-4 suppression.

Often, pancreatic and myocyte cells are employed in cell-based tests to find DPP-4 inhibitors. The downstream signalling of GLP-1 in pancreatic cells may serve as an indication or biomarker of DPP-4 activity since cells in pancreatic islets are a major GLP-1 target (147). GLP-1 also reduces the inflammation that lipopolysaccharide (LPS) causes in cardiomyocytes. DPP-4 activity may be inferred from the alterations in inflammatory signalling, such as NF-B, ERK, and TNF, in LPS-induced cardiomyocytes (148). However, because in vivo pharmacodynamic and pharmacokinetic aspects are not taken into account, the findings of cell-based tests may not be a true representation of the reality scenario. But prior to clinical or animal studies, direct effect on target cells may be highly useful in describing intracellular dynamics.

Based on the features of T-cell activation and inflammation, DPP-4 inhibitors have been recognised as a possible treatment for autoimmune illnesses. Notably, autoimmune animal models provide a platform for assessing the in vivo effectiveness of DPP-4 inhibitors when used over an extended period of time (149). Alternatively, diabetic animal models may be used to test the effectiveness of DPP-4 inhibitors in vivo, despite the fact that DPP-4 can degrade GLP-1, desensitising the body to insulin and decreasing production. The greatest enduring drawback of in vivo testing is that, although it is more relevant to clinical settings, only end-point effects may be seen in pre-testing drug candidates. Understanding the potential hypoglycemic process may require information from both direct enzymatic testing and in vitro experiments (150).

18.3-Novel DPP-4 inhibitors derived from natural substances

From the end of the 1990s to the beginning of the 2000s, investigations on the effects of DPP-4 were mostly focused on the immunological, endocrine, and neural systems. According to research published in 2006, incretin is the molecular target of DPP-4, indicating the potential use of DPP-4 inhibitors in the treatment of diabetes. As a result, the quest for anti-diabetic DPP-4 inhibitors has adopted a new paradigm as a result of the study on diabetes (151). Only a relatively small number of natural DPP-4 inhibitors from different sources or origins have been reported so far (Table 8). The following is a summary of natural DPP-4 inhibitors from various sources that were discovered using various methods for screening the chemical to hit the target. In addition to being derived from plants, DPP-4 inhibitors from animals and microorganisms also fall under single subclasses and are, respectively, peptides and macrolides. Interestingly, terpenoids, peptides, phenolics, and flavonoids are the most common categories of DPP-4 inhibitors (152). These results suggest that alkaloids are not effective as DPP-4 inhibitors or that their potential uses in DDP4 inhibition have not been fully investigated. In addition to pure chemicals, several unprocessed natural extracts or protein hydrolysates may also inhibit DPP-4. For instance, methanol extracts of Ficus benghalensis, Syzigium cumini, Ocimum sanctum, and Eucalyptus sp. have been shown to exhibit DPP-4 inhibitory properties (153). The anti-diabetic effectiveness of traditional Chinese medicine's Schizandra chinensis decoction In vivo tests using Bail’s Coptis chinensis, Psidium guajava L., and Morus alba L. have shown that these plants can inhibit DPP-4. In enzymatic tests, the protein hydrolysates from whey, barley, and yam may decrease DPP-4 activity (154). The strongest DPP-4 inhibitory peptide sequences, including Ala-Pro, Leu-Pro-Val-Pro-Gln, Trp-Ser-Gly, and Phe-Ser-Asp, have been identified using molecular sieving. However, given that physiological control of DPP-4 is far more complex than can be determined from bench-top research, these findings from in vitro enzymatic tests

cannot be taken to indicate a positive future. Thus, in order to corroborate the findings of direct enzymatic testing for novel candidates or hits, such as in vivo studies to establish their real therapeutic qualities when compared with clinical drugs, additional validation is required (155).

Structure subclass	Compound name	Source	Testing method
Plant origin			
Alkaloids	Ephedrine	Ephedra spp.	Enzymatic
	Berberine	Coptis chinensis	Enzymatic
Diarylheptanoid	Calebin A	Curcuma longa	Enzymatic
Flavonoids	Chrysin	Passiflora caerulea	In vitro
	Kaempferol, Kaempferol 7-O-A-L-Rhamnoside, Vitexin, Lepidoside, Rutin	Smilax china L.	Enzymatic
	Aspalathin	Aspalathus linearis	In vivo
glycoside	Linustatins A, Linustatins B, Linustatins C, Linustatins D, Linustatins E	Linum usitatissimum L.	Enzymatic
Peptide	Soybean hydrolysate	Glycine max	Ex vivo
	Lupin hydrolysate	Lupinus spp	Ex vivo
	AP peptide, IPA Peptide	Euphausia superba	Enzymatic
Phenolics	Emodin	Rheum palmatum Linn	n vivo
	Salvianolic Acid C	Xiaokean formula	Enzymatic
	(+)-Vitisin A	Vitis -thunbergii var. taiwaniana	Enzymatic
	(–)-Vitisin B		
	Syringic Acid 4-O-B-D-Glucopyranosyl- (1→5)-A-L-Rhamnopyranoside, Eight phenolic glycosides, Two phenolic acids	Magnolia officinalis	Enzymatic
Sterol	Stigmasterol	Fagonia cretica	Enzymatic
Terpenoids	16-hydroxycleroda-3,13-dien-15,16-olide	Polyalthia longifolia	In vivo
	Quinovic Acid, Quinovic acid-3B-O-B-D-glycopyranoside	Fagonia cretica	Enzymatic
	Quinovic acid-3B-O-B-D-glucopyranosyl-(28→1)-B-D-glucopyranosyl ester		
	Ginsenoside Rg, Timosaponin AI	Xiaokean formula	Enzymatic
	Two norsesquiterpenoids	Magnolia officinalis	Enzymatic
	Lupeo	Hedera nepalensis	Enzymatic
Xanthonoi	Mangiferin	Magnifera indica	In vivo
Animal origin			
Peptide	LPVPQ peptide, IPM peptide	milk	Enzymatic
	WSG peptide, FSD peptide	Barbus sp.	Enzymatic
Microbial origin			
Macrolide	Grassypeptolide A	marine	In vitro
FSD, Phe-Ser-Asp; IPM, Ile-Pro-Met; LPVPQ, Lys-Pro-Val-Pro-Gln; WSG, Trp-Ser-Gly.			

18.4-Using DPP-4 inhibitors with caution

The biological processes, test procedures, and known natural DPP-4 inhibitors that are allegedly used to treat diabetes were covered in earlier sections. However, because of its interdependence with the immune response and endothelial activities, DPP-4 inhibition may have unintended consequences. In fact, recent reviews have examined the functions of DPP-4 in carcinogenesis and progression, respectively (156). DPP-4 inhibitors may unquestionably slow the spread of lung and pancreatic cancer and increase overall survival. DPP-4 inhibition would have the opposite effect in breast cancer, prostate cancer, and endometrial carcinoma, which increases the spread of the disease. However, it is known that DPP-4 inhibition in carcinogenesis and tumour formation in site-specific tumours should be taken into consideration even if the function of DPP-4 inhibition in cancer therapy is unclear (157).

Opportunistic infection is another problem with DPP-4 suppression, in addition to the growth of malignancy. The author described a 69-year-old diabetic patient who, after taking vildagliptin for a week due to hypercytokinemia, experienced a fever. There are several chemokines that may act as DPP-4 substrates, including CXCL3, CXCL4, CXCL 5, and CXCL 10. After reviewing the Longitudinal Health Insurance Database 2000, researchers discovered that DM patients receiving short-term DPP-4 inhibitor medication had a greater chance of contracting herpes zoster than patients who were not receiving DPP-4 treatment (158). DPP4 levels are negatively associated with the onset of both celiac disease and Hashimoto's thyroiditis (see above), indicating that DPP-4 suppression might hasten the development of illness. Crohn's disease and ulcerative colitis are together referred to as "inflammatory bowel disease," which is brought on by immune cell filtration or opportunistic infection (159). According to a meta-analysis, DPP-4 inhibition may raise the likelihood of developing Crohn's disease. DPP-4 inhibitors may be used to treat diabetes mellitus; however, their adverse effects on other immunological diseases or cancer should be carefully examined (160).

19-Perspectives and prospective studies

In vitro enzymatic and cell assays, in vivo animal testing, and the impact of virtual screening using computational biology or informatics together provide a promising method to find potential candidates or hits for accelerating the preclinical development process **(Figure 7).** However, little attention has been put into profiling the ADME/Tox characteristics of DDP-4 inhibitors, despite the fact that poor or unfavourable medication absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) features contribute significantly to drug attrition (161). In order to reduce late-stage failures, it is thus required to forecast ADME and toxic parameters throughout the virtual screening process. This should be done by using strategies that can take into account the unstructured character of DDP-4 (126).

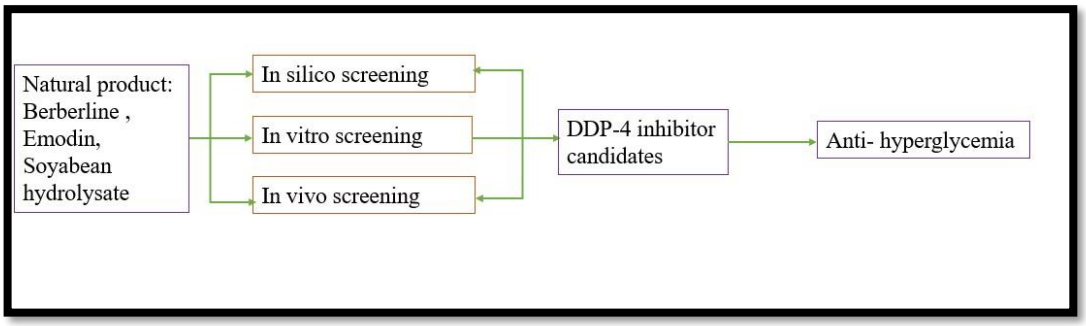

Figure -7 Natural product effects on DPP-4 inhibition and screening techniques

Conclusion

The use of metformin, sulfonylureas, and thiazolidinediones in addition to DPP-4 inhibitors is advised since they are potential novel treatments for type 2 diabetes mellitus. More long-term data about security and cardiovascular health are required.

DPP-4 inhibitors are oral diabetic medicines that block the action of the DPP-4 enzyme. This enzyme influences glucose regulation by improving the incretin system's performance. They have a reduced risk of hypoglycemia, little weight gain, and are well tolerated, lowering blood sugar and HbA1c levels in a clinically significant manner. They have the same impact on HbA1c as other oral diabetic medications and may be taken without changing the dosage. Although DPP-4 inhibitors are effective diabetes medications, it is still unclear what their long-term effects will be and how long they will persist. If someone has chronic renal disease and is at risk for low blood sugar, linagliptin may be a useful first line of therapy, but the price and potential cardiac risks should be considered before prescribing this course of action. Consider risk factors, such as a history of heart failure or chronic renal disease.

A novel and potentially effective therapy for type 2 diabetes is DPP-4 inhibition. It may be used orally, is secure and well tolerated, and has long-lasting effects on glycemia. It works by causing the body to

produce more insulin and less glucagon, preventing the incretin hormone GLP-1 from becoming inactive. Additionally, it enhances how the body uses fat. DPP-4 inhibition might be used as a first-line therapy on its own or in combination with metformin in advanced stages of the condition or for those who have poor glucose tolerance.

People with type 2 diabetes may now safely and successfully manage elevated blood sugar with DPP4 inhibitors. However, it is still unclear how DPP4 inhibitors interfere with innate immunity in a manner that reduces its potency. The DPP4 protein has been shown to alter form in studies, which may help to explain why various DPP4 inhibitors have varying effects.

SUs and DPP-4 inhibitors are two widely used classes of second-line medications. DPP-4 inhibitors have been demonstrated not to increase the risk of heart disease, don't influence weight, and often have fewer side effects than SUs. For certain people, they are superior to SUs, but as patients need more diabetic medication, they may be considered the superior option more often. Drug costs may not matter as much in the future.

Because they are less likely to result in low blood sugar and function in a manner that complements first-line therapies, DPP4i are often used as a second-line therapy for T2DM. Glycaemic effectiveness has been improved without requiring patients to take more tablets by co-formulating fixed-dose combinations of DPP4i with other widely used medications. Cardiovascular safety has been shown; however, DPP4i is silent on the subject. For those who do or do not exhibit symptoms of atherosclerotic cardiovascular disease, chronic renal disease, or heart failure, the most recent consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes offers conflicting counsel. For the majority of T2DM patients, DPP4i are safe and effective, and it is believed that their positive therapeutic profile will help patients achieve their glycaemic goals. Some patents are due to expire, making DPP4i more accessible as they transition from a proprietary to a generic state.

Currently prescribed medications for type 2 diabetes act by increasing the body's production of insulin, reducing its resistance to it, and slowing down the digestion of glucose. These medications are effective in the short- to medium-term, but neither they nor the disease's long-term negative effects prevent it from growing worse. DPP-4 inhibitors help the body regulate blood sugar levels in a healthy manner. For those who don't have adequate control over their blood sugar, are at a high risk of hypoglycaemic episodes, don't want to put on weight, or for whom other anti-diabetic medications don't work well or are risky, they may be taken in conjunction with metformin or sulphonylureas. A daily oral dosage that has no significant negative effects ensures consistent management of the metabolism. There is a lot of future potential for this therapeutic course.

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