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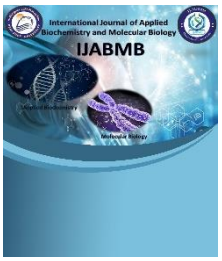

Pharmacological Insights into Dipeptidyl Peptidase-4 Inhibitors: Therapeutic Applications and Future Perspectives

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Running Title: Pharmacological Insights into DPP-4 Inhibitors

Abstract

Dipeptidyl peptidase-4 inhibitors (DPP-4Is) are considered a fundamental group of oral hypoglycemic drugs that are extensively utilized in type 2 diabetes mellitus (T2DM) treatment, primarily by modulating incretin hormones to enhance glycemic control, a process that is described as the incretin effect.

Accumulating experimental and clinical data suggest that these drugs can extend benefits beyond glucose-lowering effects, exhibiting potential positive feedback on cardiovascular health, kidneys, and liver. It also possesses an interesting role in COVID-19 management and Alzheimer's disease. Beyond their well-established role in glycemic control, DPP-4 inhibitors may help to modulate other risk factors by offering organ protection, highlighting the importance of continued rigorous research in this area.

This review summarizes the published preclinical and clinical research discussing the pharmacological features of DPP-4Is, along with their safety profiles and potential side effects. Moreover, pharmacokinetic properties, mechanisms of action, and therapeutic applications of approved DPP-4Is, including Saxagliptin, Sitagliptin, Vildagliptin, Alogliptin, and Linagliptin, were also discussed in this review.

Keywords

Incretins; Type 2 Diabetes Mellitus; Alzheimer`s disease; Nephroprotective; COVID-19.

1. Introduction

Drugs that target incretin hormones have proven their effectiveness in improving the effectiveness of therapy in type 2 diabetes patients (1). This effect is mediated by a physiological phenomenon called the incretin effect, where the body produces more insulin in response to glucose taken by mouth than to the same amount of glucose introduced via injection. Studies have shown that insulin secretion after oral glucose administration can be three times higher than that resulting from intravenous glucose (2), highlighting the vital role of intestinal hormones in regulating blood sugar levels.

Two of the primary hormones involved in the action of incretins are glucagon like peptide-1(GLP-1) and gastric inhibitory peptide (GIP). Both of them are released from specific cells in the intestine postprandially and are critically involved in regulating blood sugar. GLP-1 and GIP potentiate insulin production by beta cells found in the pancreas when glucose levels are significantly high. They also reduce glucagon secretion and slow gastric emptying, which also helps promote feelings of fullness (3).

Additionally, they do not remain in the body for a long time. This is due to an enzyme called DPP-4, which works very quickly and achieves its effectiveness within a very short time. This enzyme acts on the oligopeptides containing proline or alanine residues from the third position onward, following the second amino acid from the N-terminus, rendering them ineffective within minutes (4). What's interesting is that DPP-4 doesn't just work on these hormones; it also breaks down more than 40 other active substances in the body, including some hormones, neurotransmitters, and cytokines (5). This makes maintaining the effectiveness of these regulatory substances in the body is difficult.

DPP-4 is part of an extensive group of enzymes of which DPP-8, DPP-9, and fibroblast activation protein (FAP) are members (6). It is a 766-amino-acid trans membrane glycoprotein, referred to as cluster of differentiation 26 (CD26) as well (7). Functionally, DPP-4 is a serine protease found on the

surfaces of epithelial and endothelial cells, as well as circulating freely in the bloodstream (8). It is present in many tissues like the brain, lungs, liver, kidneys, and immune cells (9).

It has been shown that DPP-4 has two important roles; firstly, it acts as a membrane-bound protein that can interact with other cellular proteins to facilitate intracellular signal transduction. Secondly, it acts as an enzymatic agent that cleaves dipeptides from specific substrates. Its widespread expression and multifunctionality underscore its importance in both metabolic regulation and immune responses (9). Consequently, inhibiting DPP-4 has become a therapeutic action by mediating GLP-1 and GIP degradation to prolong their effects in diabetes management. This strategy also aims to explore their potential benefits in other physiological processes.

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin, mentioned in recent studies, are oral DPP-4Is that are characterized by decreasing blood glucose levels with no risk of hypoglycemic phenomenon and no effect on body weight, and their chemical structures are illustrated in Figure 1.

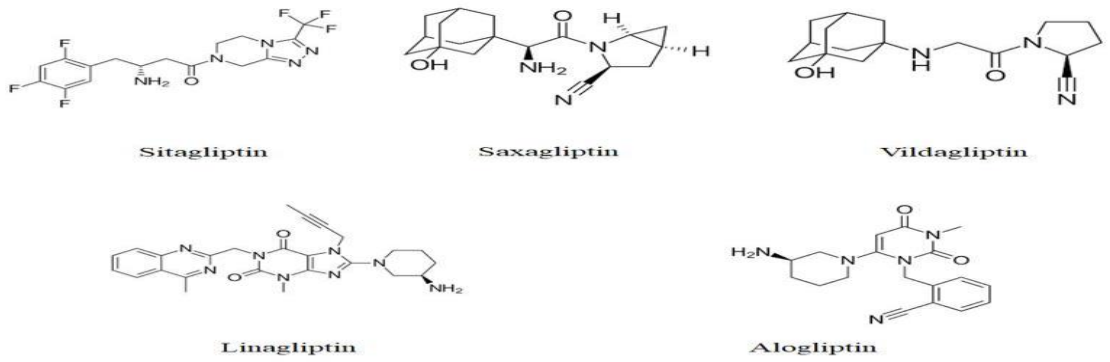

Figure 1: Chemical structure of DPP-4Is (10).

2. Pharmacokinetics of DPP-4Is

An overview of the pharmacokinetic properties of DPP-4Is is collected. Concerning sitagliptin, it is taken once daily due to its long half-life. The insufficiency of active metabolites and their renal excretion made it more important to reduce the sitagliptin dose in moderate or severe cases (but not mild) of renal injury (11, 12).

By contrast, vildagliptin is taken twice daily due to its shorter half-life. Vildagliptin demonstrates limited renal elimination in its active form, whereas its primary metabolite, pharmacologically inactive, is more readily excreted. As a result, dose modification is generally unnecessary in mild renal injury patients (13-15).

Moreover, Saxagliptin is a drug with a short elimination half-life, but it provides the added advantage of producing an active metabolite capable of inhibiting DPP-4 with half the efficacy of the parent drug, allowing it to be used as a once-daily dose. Since both the parent drug and metabolite are eliminated with the help of the kidneys, dose modification is necessary in individuals with renal injury (16-18). Furthermore, saxagliptin differs from other DPP-4Is in its potential for drug interactions via liver enzymes, particularly with the cytochrome P450 system. This necessitates a dose adjustment when used with strong cytochrome P450 3A4 (CYP3A4) inhibitors(19).

Alogliptin's pharmacokinetics are remarkably similar to sitagliptin (20-22). It is rapidly absorbed when taken orally and taking it with food does not significantly affect its bioavailability. Approximately 20 to 30 percent of alogliptin is bound to blood proteins, and its half-life is approximately 21 hours at the maximum recommended dose of 25 mg. Alogliptin is mostly excreted unchanged in the urine, and its hepatic metabolism is low. Its pharmacokinetics is similar in both healthy individuals and type 2 diabetes patients and is not affected by age or race.

In general, mild to moderate renal or hepatic impairment cases do not require dose modification. However, dose modification becomes necessary in cases of severe renal impairment, and it is not preferable in cases of acute hepatic impairment due to limited available studies.

Linagliptin has unique pharmacokinetic properties; it is highly bound to plasma proteins (over 80% at the clinically effective dose), has an extended elimination half-life, and has virtually non-negligible renal excretion, distinguishing it from other available DPP-4Is (25-23). In practice, as displayed in Table 1, it is noted that vildagliptin requires two doses daily (50 mg twice a day), unlike other drugs such as sitagliptin (100 mg once a day), saxagliptin (5 mg once a day), alogliptin (12.5–25 mg once a day), and linagliptin (5 mg once a day).

Table 1. Comparison between various approved DPP-4Is

Drug	First approved	Half-life	Dosing Frequency	Renal Excretion	Dose Adjustment in Renal Impairment
Sitagliptin (26, 27)	2006 (USA)	Long (12h)	Once daily (100mg)	High	Yes (moderate/severe RI)
Vildagliptin (28)	2007 (European Union)	Short (3h)	Twice daily (50 mg BID)	Low	No (mild RI); Yes (moderate/severe RI)
Saxagliptin (29)	2009 (USA)	Short (2.5h)	Once daily (5mg)	Moderate	Yes (with CYP3A4 inhibitors)
Alogliptin (30, 31)	2010 (Japan)	Long (21h)	Once daily (12.5-25mg)	High (unchange)	Yes (severe RI only)
Linagliptin (32)	2011 (USA)	Very long	Once daily (5mg)	Negligible	No

3. Mechanisms of action of DPP-4Is

Regulating glucose metabolism is one important role of the DPP-4 enzyme. It acts by influencing incretin hormones. These hormones serve a crucial function in preserving blood glucose balance by stimulating insulin production and inhibiting glucagon secretion(33). GLP-1 is secreted from the hormone-secreting L cells of the small intestine and contributes to blood glucose level reduction by increasing insulin secretion, decreasing glucagon levels, and delaying gastric emptying (34). However, its half-life is very short, less than two minutes(35). GIP, on the other hand, is released from K cells that reside in the stomach and nearby small intestine and has a half-life of approximately seven minutes in healthy volunteers and approximately five minutes in patients with type 2 diabetes (35-37). As illustrated in Figure 2, following meals, both hormones are released into the blood rapidly. Once they meet the DPP-4 enzyme, it degrades them. That's why they have a short half-life. So, inhibiting this enzyme became an issue to prolong the period during which these hormones remain active in the body. This strategy potentiates insulin secretion from pancreatic beta cells and reduces glucagon secretion, leading to improved control of blood glucose levels after eating and during fasting (33).

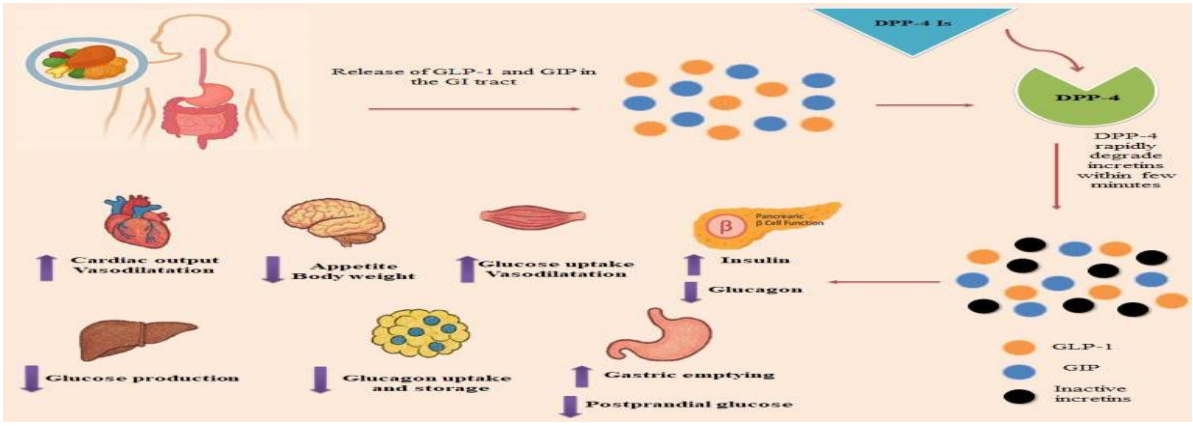

Figure 2. Physiological effects of DPP-4Is. GLP-1: glucagon-like peptide-1, GIP: gastric inhibitory peptide, GI tract: Gastrointestinal tract, DPP-4Is: Dipeptidyl Peptidase 4 Inhibitors. The upward-pointing blue arrow indicates an increase, and the downward-pointing blue arrow indicates a decrease.

4- Therapeutic applications

DPP-4Is enhance glucose-dependent insulin secretion by preventing the breakdown of GLP-1 and GIP, improving glycemic control without significant hypoglycemic risk (38). In addition to their glucose-lowering properties, this drug class also exhibits antihypertensive (39), anti-inflammatory, antiapoptotic, and immunomodulatory actions that benefit the heart, liver, kidney, and blood vessels, regardless of their effects on the incretin system (40), as illustrated in Figure 3.

Some research suggests that these medications may be helpful for patients who develop a recent diabetes diagnosis following kidney or liver transplantation, thanks to their broad therapeutic benefits (40). These agents can be prescribed either as standalone treatments or in combination with other antidiabetic medications (41, 42). Common combination partners include metformin (43), sulfonylureas (44), thiazolidinediones (45), and insulin (46).

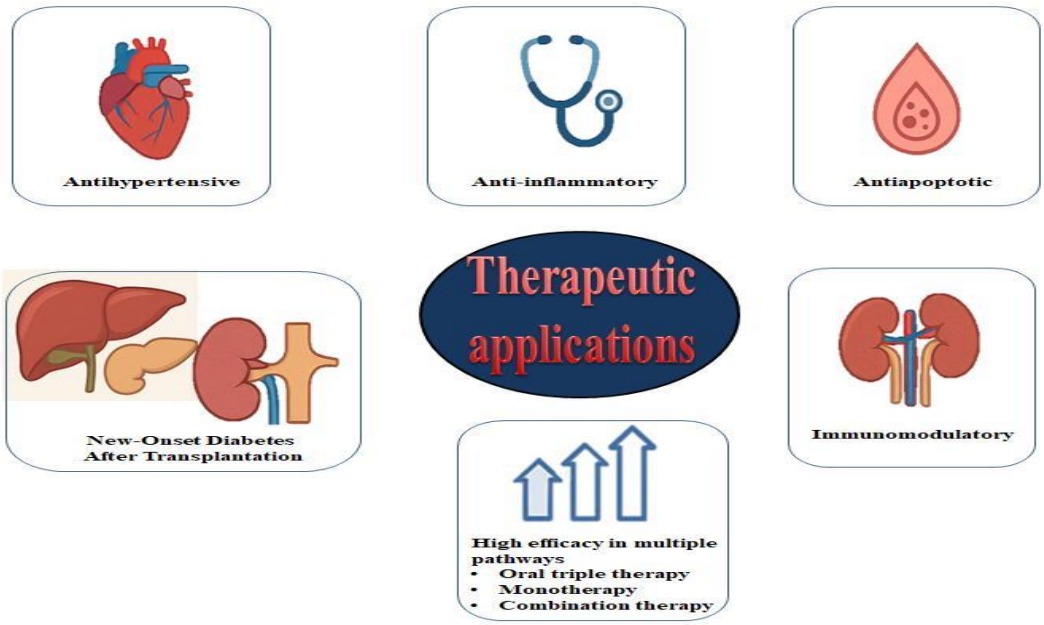

Figure 3. Therapeutic applications of DPP-4Is.

5- Therapeutic potential of DPP-4Is on experimental and clinical studies

5.1.Cardioprotective Effects

DPP-4Is' potential cardiovascular benefits beyond glycemic control have recently acquired popularity(47). Clinical and experimental outcomes recommended that medications like sitagliptin, vildagliptin, and saxagliptin may possess positive feedback on cardiac function and vascular integrity(50-48). If we talk about sitagliptin, it has shown overwhelming success in improving myocardial performance and coronary perfusion in patients suffering from coronary artery disease, as evidenced through stress echocardiography(51). Preclinical studies indicate that the process of DPP-4 inhibition enhances levels of stromal cell-derived factor 1-alpha (SDF-1α), facilitating mobilization of endothelial progenitor cells (EPCs) that support vascular repair and angiogenesis (8, 52). Despite some studies paying particular attention to a neutral cardiovascular safety profile overall, other investigations have raised concerns about increased hospitalization for heart failure in specific subpopulations treated with certain DPP-4Is, particularly saxagliptin (48) .However, a comprehensive review of multiple clinical trials generally found no heightened cardiovascular risk, emphasizing the need for more robust, targeted studies (53). Vascular health support is another benefit of DPP-4 inhibition. It occurs by modulating nitric oxide-mediated pathways, reducing blood pressure, and mitigating low-grade systemic inflammation, a known contributor to atherogenesis(54). Animal studies also shared a role in reducing inflammatory cell infiltration in visceral fat, potentially curbing the progression of atherosclerosis (55).

5.2. Nephroprotective Effects

The kidneys might be another winner here. Nascent data lit the way for the nephroprotective role of DPP-4Is (56). Their ability to reduce systemic inflammation, modulate oxidative stress, and regulate renal hemodynamics makes them particularly relevant in the context of

kidney disease associated with diabetes(57). Preclinical models have established that DPP-4 inhibition can lessen glomerular injury and tubular apoptosis, likely via increasing regulation of endogenous GLP-1 signaling and downregulation of pro-inflammatory cytokines, TNF-α (58). While specific large-scale trials on renal endpoints are still limited, few studies have pointed in a hopeful direction, which include renal function markers stabilization and albuminuria reduction when DPP-4Is are added to standard anti-diabetic regimens (59). The lack of need for dose adjustments in renal impairment, notably with linagliptin, further adds to their clinical convenience in nephropathy-prone populations and makes it more practical in a real-world setting (60).

5.3. Hepatoprotective Effects

Preclinical investigations have also revealed a beneficial influence of DPP-4 inhibition on hepatic metabolism and inflammation. By enhancing insulin sensitivity and reducing hepatic steatosis, DPP-4Is may hold great expectations in managing non-alcoholic fatty liver disease (NAFLD), generally connected to T2DM(61).

The anti-inflammatory properties of these agents, coupled with their impact on lipid metabolism, contribute to an improved hepatic profile in diabetic models(62). While human clinical evidence is still catching up, some studies indicate improvement in liver function and reduced intrahepatic fat accumulation in patients treated with DPP-4Is, especially vildagliptin ,63). (64These effects seem to be mediated through GLP-1-dependent and independent pathways.

5.4. COVID-19 Management

Beyond DPP4's metabolic role, emerging data indicate that DPP-4 may also be involved in the pathogenesis of specific coronaviruses. Despite angiotensin-converting enzyme 2 (ACE2) being the principle receptor for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), DPP-4, or CD26, has been implicated as an active receptor for middle east respiratory syndrome coronavirus (MERS-Cov) and may contribute to the immune dysregulation observed in

coronavirus disease 2019 (COVID-19) (65, 66). DPP-4Is might possess beneficial effects in COVID-19 patients undergoing treatment for T2DM by mitigating exaggerated inflammatory response characteristic of severe disease (67, 68). These agents may reduce concentrations of pro-inflammatory cytokines including IL-6 and TNF-α, modulate immune cell activity, and limit tissue injury through anti-inflammatory and anti-apoptotic mechanisms (69, 70). Observational studies have reported improved clinical outcomes and lower mortality rates in diabetic patients treated with DPP-4Is during COVID-19 infection, although further randomized trials are necessary to validate these findings (71, 72).

5.5. Immunological consequences

DPP-4Is have also displayed potential immunomodulatory effects; for instance, sitagliptin has demonstrated anti-inflammatory activities in both preclinical and clinical settings (73). Although saxagliptin has been associated with minor lymphocyte count reductions, immune function remained intact in experimental models (74, 75). Moreover, animal and human studies have highlighted the capacity of DPP-4Is to enhance wound healing and reduce inflammatory mediators, positioning them as potential agents in diabetic wound management. Linagliptin, for instance, has been shown to accelerate epithelial regeneration and mitigate inflammation in diabetic wounds (76).

5.6. Lipid profile effects

Beyond their metabolic and organ-protective roles, DPP-4Is have shown mild but favorable effects on lipid profiles, such as reductions in total cholesterol and triglycerides, as demonstrated in meta-analyses. (77). Collectively, all these findings uncovered the multifaceted therapeutic potential of DPP-4Is, extending their utility well beyond glucose regulation, as summarized in Figure 4 and stated in Table 2. Nonetheless, large-scale, long-term trials are essential to fully validate these promising organ-protective and systemic effects and to establish firm clinical guidelines for their broader use.

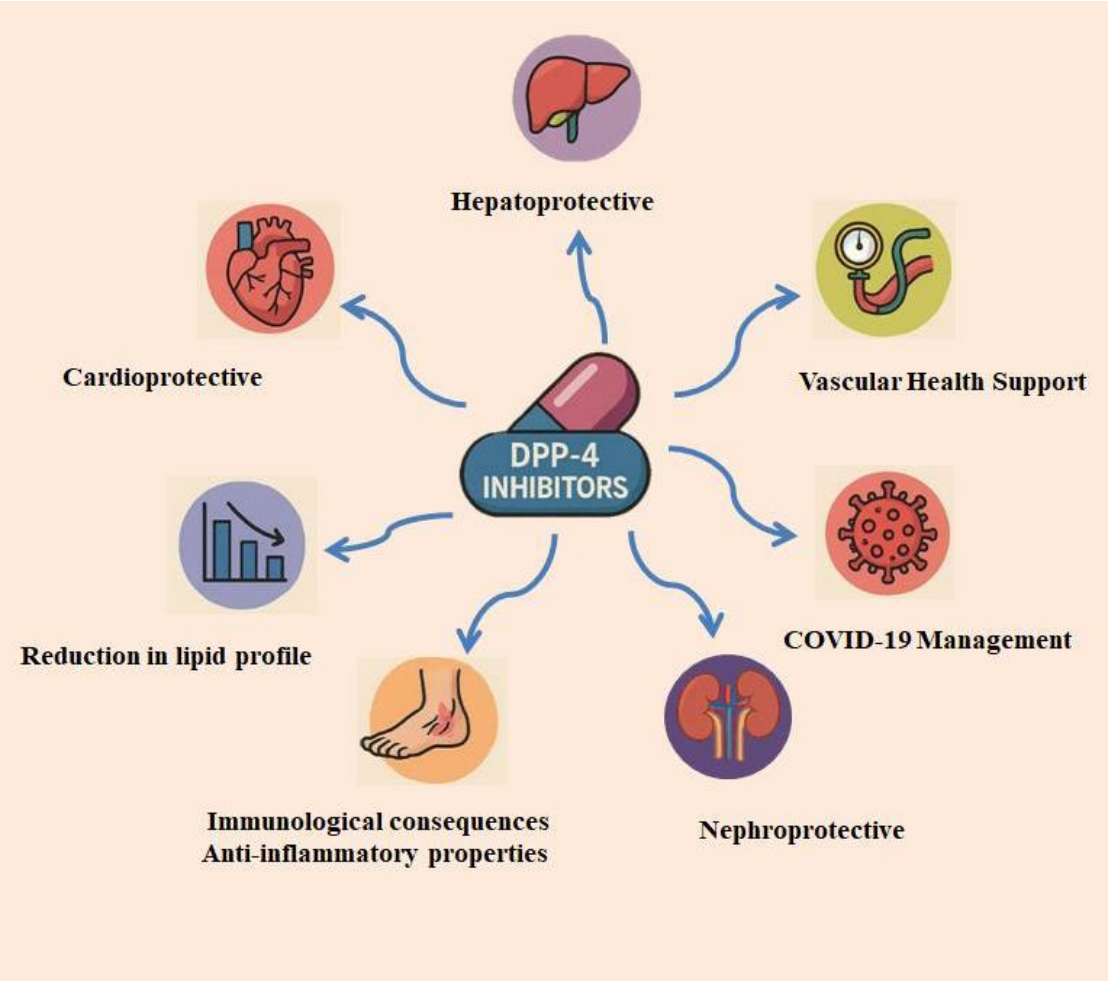

Figure 4: Therapeutic potential of DPP-4Is

Table 2. Summary of Dipeptidylpeptidase-4 inhibitors' pharmacological actions in preclinical and clinical studies

Pharmacological action	Aim of study	Outcomes
Anti-inflammatory (78)	To evaluate the reduction of inflammatory cytokines (TNF-α, IL-1β)	DPP-4Is significantly reduces inflammatory markers and oxidative stress
Antioxidant(79)	To assess oxidative stress markers and protective enzymes	Upregulation of Nrf2/HO-1 signaling and reduction in ROS
Anti-apoptotic (80)	To determine apoptosis-related protein expression(caspase-3)	Decreased cleaved caspase-3 expression and increased Bcl-2
Renal protection (56, 81)	To investigate renal histopathology ad serum creatinine/BUN levels	Improvement in renal histology and biochemical kidney function markers
Glycemic control (82)	To evaluate HbA1c and fasting glucose in diabetic patients	Significant reduction in HbA1c and fasting glucose levels
Cardiovascular protection (47, 83)	To assess cardiovascular event rates and blood pressure	Neutral to mild improvement in cardiovascular outcomes
Neuroprotective effect (80, 84, 85)	Determine neuroprotection in models of Alzheimer`s, Parkinson's, and cognitive dysfunction	Enhanced cognitive performance, reduced amyloid plaques, and neuroinflammation

DPP-4Is: Dipeptidyl Peptidase-4 Inhibitors, TNF-α: Tumor Necrosis Factor-alpha, IL-1β: Interleukin-1 beta, Nrf2: Nuclear Factor Erythroid 2–Related Factor 2, HO-1: Heme Oxygenase-1, ROS: Reactive Oxygen Species, Bcl-2: B-cell lymphoma 2 (anti-apoptotic protein), BUN: Blood Urea Nitrogen, HbA1c: Hemoglobin A1c (Glycated Hemoglobin).

6. Adverse effects of DPP-4Is

However, gliptins are generally well tolerated, with a low incidence of hypoglycemic events, and no significant impact on weight. Nevertheless, the likelihood of hypoglycemic events rises once these drugs are combined with sulfonylureas (86).

The greatest concerning frequently reported complications of DPP-4Is such as sitagliptin and saxagliptin include upper respiratory tract infections, nasopharyngitis, headaches, urinary tract infections, and joint pain (34). Additionally, prescribing information for most DPP-4Is mentions the possibility of immune-mediated hypersensitivity ranging from

angioedema to life-threatening anaphylaxis (87). Post-marketing data have linked sitagliptin with rare diagnosis of Stevens-Johnson syndrome(34). There are also documented reports of acute pancreatitis, ranging from mild to severe, including hemorrhagic and necrotizing forms—associated with sitagliptin, vildagliptin, and saxagliptin (87); however, a definitive causal relationship has not been established (88). A case series from Japan even described four instances of acquired haemophilia A in patients receiving DPP-4Is (89). In large clinical trials, DPP-4Is (including alogliptin, sitagliptin, saxagliptin, and linagliptin) failed to reveal a significant increase in the risk of fatal cardiovascular events, non-lethal heart attack, or non-lethal cerebrovascular event when evaluated against placebo in T2DM patients (90, 91). However, saxagliptin was linked to an increased risk of heart failure-related hospitalization (48).

7. Conclusion

It could be emphasized that DPP-4Is seem to wear many hats. From heart and kidney protection to liver health and wound care, their reach goes well beyond blood sugar management. Furthermore, ongoing research suggests additional therapeutic potential in protecting cardiovascular, nervous, renal, and hepatic systems. It is worth noting that their favorable pharmacokinetic properties, once-daily dosing, and minimal risk of hypoglycemia render them appropriate for diverse patients. While generally safe, attention should be paid to rare but notable adverse effects. Overall, DPP-4Is remains a valuable component of the antidiabetic pharmacopoeia with evolving roles in chronic disease management, and these findings- while exciting- need to be backed up by larger and longer-term clinical trials to further elucidate their durable efficacy and a consistent safety profile, especially when used alongside other therapies and among patients with comorbid conditions.

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