RESEARCH PAPER

Dipeptidyl Peptidase-Iv As A Multifunctional Enzyme: A Comprehensive Review Of Physiology, Pathobiology, And Pharmacological Targeting

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Abstract

Background: Dipeptidyl peptidase-iv (dpp-iv), a serine protease essential to biological systems, is involved in metabolic regulation, immunological response, and its implications in various pathological conditions, most notably type 2 diabetes mellitus (t2dm) and malignancies. The article explores the structure, function, and regulation of dpp-iv, emphasizing its numerous roles in health and illness.

Materials and Methods: This study includes comprehensive searches in pubmed/medline, scopus, cochrane database of systematic reviews, published review papers, and clinical trials databases (us national library of medicine) with no time constraints.

Results and Discussion: Dpp-iv's primary part is maintaining glucose homeostasis by modulating incretin hormones, with implications extending to immunological responses, tissue remodelling, cancer, inflammation, neurological processes, and wound healing. Dpp-iv regulates at numerous levels, from transcriptional control to post-translational modifications and interactions with other proteins. Dpp-iv inhibitors, which are pharmacological drugs that decrease their activity, have sparked considerable attention, particularly in treating t2dm. The incidence of t2dm and its expected rise highlights the significance of effective treatment targets. Beyond diabetic management, new research suggests that dpp-iv inhibitors may have cardiovascular advantages, reno-protective effects, anti-inflammatory qualities, and neuroprotective capabilities. Hence, this article thoroughly explains dpp-iv, detailing its structural, functional, and regulatory characteristics.

Keywords: Dpp-Iv Enzyme, Type 2 Diabetes Mellitus, Incretin Hormones, Dpp-Iv Inhibitors, Metabolic Regulation.

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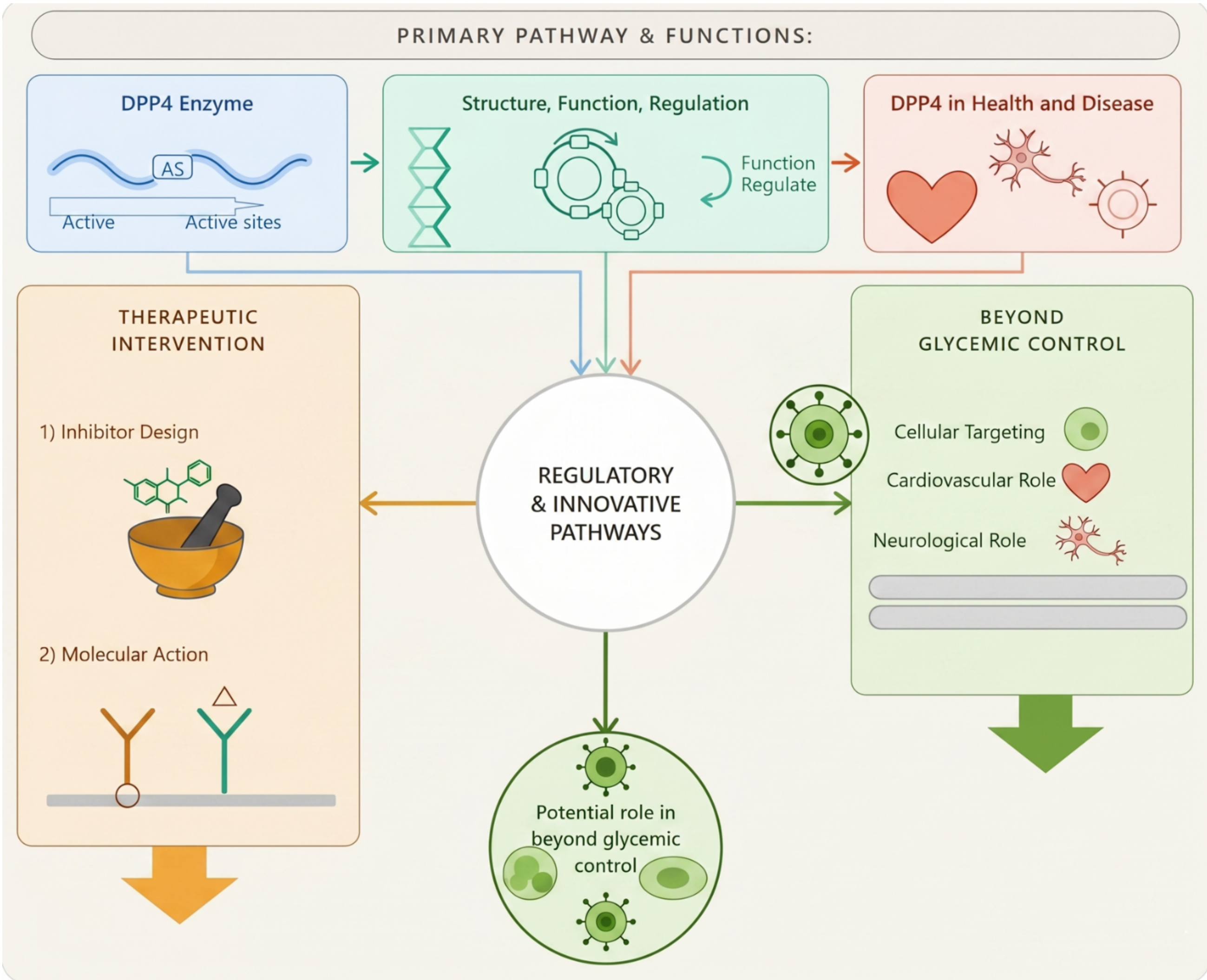

Graphical Abstract

INTRODUCTION

Enzymes, fundamental components of biological systems, facilitate several physiological processes in living organisms (Nguyen et al., 2018). DPP-IV is one such enzyme that has attracted substantial interest in recent years for its numerous and complicated roles in both health and sickness. DPP-IV (CD26), is a serine protease that cleaves dipeptides from the N-terminus of different proteins and peptides (Enz et al., 2019). The involvement of this entity in metabolic regulation and immune response, as well as its potential importance in numerous clinical disorders, including type 2 diabetes and malignant cancers, underlined its variety. This enzyme has become a focus of significant investigation since it offers a potential target for treatments in various clinical diseases. T2DM is a commonly encountered metabolic and complex chronic illness categorized by the presence of insulin resistance and compromised functionality of beta cells in pancreas (Röhrborn et al., 2015). According to forecasts from the International Diabetic Federation (IDF), the population affected by T2DM will be about 643 million by 2030, rising to 783 million by 2045 (IDF, 2021) (H. Sun et al., 2022). Maintaining glycemic levels is crucial to mitigate the risk of many consequences, such as renal impairment, and neuropathy, retinopathy and cardiovascular diseases. To control T2DM, various pharmacological therapies have been developed over time. DPP-IV inhibitors have garnered considerable interest owing to their distinctive mode of action and advantageous safety profile (Kushwaha et al., 2014). This comprehensive exploration of DPP-4 aims to provide an understanding of its structure, function, regulation, and implications in health and disease. This review will shed light on the significance of DPP-4, offering a holistic perspective on its diverse roles in various biological processes.

DPP-IV Structure:

DPP-IV is an enzyme characterized by its transmembrane glycoprotein structure, explicitly belonging to type II and known to traverse the lipid bilayer of the cellular membrane. The entity exhibits external and intracellular domains, each serving separate functional functions. The extracellular domain is essential for the enzyme's catalytic activity, whereas the intracellular domain plays a critical role in signal transduction (Gupta & Sen, 2019). DPP-IV has a beta-propeller structure in its extracellular domain that serves as the active site for enzymatic cleavage of dipeptides from the N-terminus of target substrates. The catalytic mechanism of this process is the hydrolysis of the peptide bond located between the 2nd and 3rd amino acids from the N-terminus of the substrate, resulting in the liberation of dipeptides (Ohnuma & Morimoto, 2013). (Figure 1)

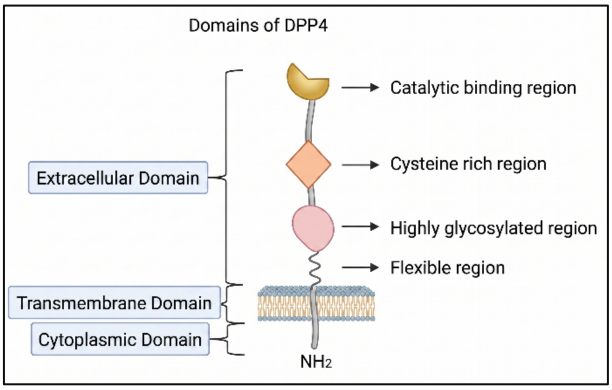

Figure 1: Structure of DPP4 enzyme

The figure shows different domains like extracellular domains which has catalytic binding pockets, Cysteine rich region, highly glycosylated region and a flexible region. It also has transmembrane domain and cytoplasmic domain having N-terminal.

DPP-IV function:

DPP-IV demonstrates a wide range of significant actions for human physiology. It is well-known that DPP-IV helps to keep glycemic index stable by regulating the activity of incretin hormones, which is its principal role (Deacon, 2018). Incretins, such as glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) are generated in response to meal consumption and promote insulin production from pancreatic beta cells (Holst, 2019). DPP-IV inactivates these incretin hormones by cleaving their N-terminal dipeptides, lowering their biological action. The aforementioned regulatory system guarantees the precise regulation of insulin release and its adaptability to fluctuations in blood glucose levels (Mulvihill & Drucker, 2014).

Additionally, it is worth mentioning that DPP-IV is not limited to only glucose metabolism (Deacon, 2019). The expression of this molecule on the surface of several immune cell types, such as T lymphocytes, B lymphocytes, and natural killer cells, contributes to its involvement in immunological regulation. The enzyme in question plays a crucial role in several cellular processes, including cell adhesion, migration, and its interaction with proteins found in the extracellular matrix (Kucuksezer et al., 2021). As a result, DPP-IV may have a role in immune responses, which could affect the onset of autoimmune diseases and immune-mediated disorders(Huang et al., 2022).The multifunctional character of DPP-IV extends beyond its involvement in metabolism and immunology. It also regulates the activity of growth factors and chemokines and is involved in tissue remodeling through its interactions with extracellular matrix components (Zhao et al., 2014). Furthermore, DPP-IV has been implicated in regulating neurological processes, wound healing mechanisms, and even the biology of tumors, potentially disrupting its expression in different forms of cancer (Busek et al., 2022).

Regulation of DPP-IV:

The control of DPP-IV activity occurs at many levels. The transcriptional regulation of the gene DPP-IV, which encodes for DPP-IV, has been observed. Multiple variables, including cytokines and hormones, have the potential to exert an impact on the expression of DPP-IV (Kim et al., 2014). For instance, previous studies have demonstrated that immune cells increase DPP-IV expression when exposed to cytokines such as IF-γ (interferon - gamma) and TNF-α (tumor necrosis factor-alpha)(Yoon et al., 2021). Post-translational changes also influence the regulation of DPP-IV activity. An example of a post-translational modification that might affect a protein's stability and functional characteristics is glycosylation, which can occur on DPP-IV(Chakraborty et al., 2014). The glycosylation patterns of DPP-IV might vary across different tissues and in response to various physiological situations, adding complexity to the regulatory systems involved. (Tomovic et al., 2019) Notably, the regulation of DPP-IV can also occur via interactions with other proteins. One example is the interaction between tissue inhibitors of metalloproteinases (TIMPs) and DPP-IV, which can lead to the modulation of DPP-IV's enzymatic activity and the consequent impact on tissue remodeling mechanisms (Ou et al., 2013). The regulation of DPP-IV encompasses not only its cellular-level control but also its systemic regulation (Rohmann et al., 2021). Various pharmaceutical agents, including DPP-4 inhibitors, have been formulated to impede the function of DPP-IV pharmacologically (Makrilakis, 2019).

DPP-IV in health and diseases:

DPP-IV, a cell surface aminopeptidase, was first identified as a T-cell differentiation antigen (CD26) (Carrasco et al., 2017) and is found on epithelial cells in the lung, liver, kidney, gut, prostate, and placenta. (Heike et al., 1988; Mizutani et al., 1985; Nemoto et al., 1999). DPP-IV can degrade bioactive peptides, cytokines, and chemokines like SDF-1α and RANTES by cleaving amino-terminal dipeptides from polypeptides with L-proline or L-alanine in position 2 (Arrebola et al., 2014; Oravecz et al., 1997; Scharpé & De Meester, 2001). Several studies have revealed that DPP-IV regulates immune-system-mediated responses, transduces signals, and interacts with extracellular matrix components (Hanski et al., 1985; Löter et al., 1995). Several studies have shown that DPP-IV may reduce tumors by inhibiting proliferation and invasiveness (Baumeier et al., 2017; Pethiyagoda et al., 2000; Tang et al., 2021; Wesley et al., 2005). A recent study by Aytac et al. found that leukemic T cells overexpressing DPP-IV, which disrupts cell cycle processes, were more sensitive to doxorubicin. Sato et al. showed that DPP-IV increased doxorubicin and etoposide-induced apoptosis sensitivity, mitochondrial pathway vulnerability, and topoisomerase II alpha expression (Aytac et al., 2001; Sato et al., 2003). DPP-IV's involvement in various biological processes underscores its significance in health and disease.

Metabolic Regulation: Within metabolic control, DPP-IV assumes a pivotal role. Certain drugs, known as DPP-IV inhibitors, have improved the treatment of type 2 diabetes by blocking DPP-IV(Ahrén & Foley, 2016). The inhibition of incretin hormone breakdown results in an augmentation of insulin production and a subsequent reduction in blood glucose levels, presenting a novel therapeutic avenue for managing diabetes (João et al., 2016). The prevalent utilization of DPP-IV inhibitors, such as vildagliptin, sitagliptin, saxagliptin, and linagliptin, within clinical practice indicates the significance attributed to this enzyme in regulating glucose homeostasis (Yin et al., 2022).

Immunology: Within the field of immunology, it is essential to note that the function of DPP-IV extends beyond its involvement in glucose metabolism (Koufakis et al., 2020). It may function in T-cell activation, cytokine production, and lymphocyte trafficking (Barreira Da Silva et al., 2015). There is a correlation between abnormal DPP-IV activity and the occurrence of autoimmune illnesses, such as rheumatoid arthritis, and immune-mediated disorders. (Pinheiro et al., 2021) Therefore, there has been an investigation into the possible use of DPP-IV inhibitors as therapeutic interventions for these disorders, as mentioned above (Gallwitz, 2019b).

Cancer: The possible implications of DPP-IV in cancer have garnered significant attention from researchers. Different types of cancer frequently alter this molecule's expression, which may influence tumor progression and metastasis (Hamidi & Ivaska, 2018). Moreover, DPP-IV has the potential to modulate the functionality of specific chemokines and growth factors that facilitate the proliferation of tumors. Preclinical trials using DPP-IV inhibitors have shown encouraging outcomes, and the possibility of targeting DPP-IV in cancer therapy is under investigation (Kawakita, Koya, et al., 2021).

Inflammation and Fibrosis: Fibrosis and inflammatory bowel illness are associated with DPP-IV (Jaenisch et al., 2022). Its significance in tissue remodeling and controlling inflammatory mediators makes it a possible therapeutic target in various diseases (Yazbeck et al., 2018).

Neurological Functions: Although the exact function DPP-IV in neurological processes remains incompletely elucidated, some investigations have posited its potential implication in neuroinflammatory responses and safeguarding neuronal integrity. Additional research is required to comprehensively understand the precise techniques and ramifications of DPP-IV inside the central nervous system (Ramesh et al., 2020).

Wound Healing: The enzyme DPP-IV controls how wounds heal, especially in skin tissue (Long et al., 2018). The phenomenon has the potential to exert an impact on the migratory behavior of cells that are actively engaged in the processes of tissue repair and regeneration (Torrecillas-Baena et al., 2022).

The many activities of DPP-IV in both physiological well-being and pathological conditions underscore its intricate nature and the possibility of employing specific treatment strategies (Patel et al., 2023). The continuous investigation into the role of DPP-IV in many physiological systems has presented novel opportunities for scholarly inquiry and the advancement of pharmaceutical interventions (Wong et al., 2014). (Table 1)

Table 1: Role of DPP4 in health and diseases

S.no.	DPP4 in health and diseases	Experimental model	Result	Reference
1.	Glucose metabolism	DPP4 knockout mice	Improves glycemic control	Baumeier et al. (2017)

2.	Fat metabolism	DPP4 knockout mice	Reduces fat mass in obesity condition	Conarello et al. (2003)
3.	Immunology	CD26-mediated signalling through constructed C-terminal deletion mutants of the human CD26 molecule and transfected into murine T cell hybridomas.	Activation of T-Cell and immune response	Fleischer (1994) & Hühn et al. (2000)
4.	Colorectal cancer	CRC patients	Elevated CD26 expression in tumors is linked to the occurrence of distant metastases and worse overall survival in individuals with colorectal cancer (CRC).	Lam et al. (2014)
5.	Breast cancer	Mouse	In vivo tumor development and metastasis are induced by DPP-4 knockdown in primary mammary tumors.	Kawakita et al. (2021)
6.	Ovarian cancer	Epithelial Ovarian carcinoma cell lines and nude mice	In vitro and in vivo studies have shown that overexpressing DPP-4 increases chemosensitivity, decreases invasive activity, and lengthens life expectancy.	Kajiyama et al. (2010)
7.	Fibrosis	Normoglycemic rats	Through membrane-bound DPP4/stromal cell-derived factor-1α-dependent local actions on angiogenesis and circulating DPP4/glucagon-like peptide-1-mediated inotropic actions diastolic left ventricular dysfunction was reversed.	Shigeta et al. (2012)
8.	Inflammation	ob/ob mice	DPP4i linagliptin improved glycemic indices and lowered liver fat and inflammation, suggesting DPP4 substrate potentiation may help liver metabolism temporarily.	Baumeier et al. (2017)
9.	Neurological function	db/db mice	In type 2 diabetes individuals, elevated DPP4 activity was found to represent a distinct risk factor for the occurrence of moderate cognitive impairment (MCI).	Sun et al. (2022)
10.	Wound healing	Randomised clinical trial NCT02742233	In vitro and in diabetic mice, DPP-4is facilitated keratinocyte migration and epithelial-mesenchymal transition by indirectly stimulating stromal cell-derived factor 1α production of fibroblasts.	Long et al. (2018)

Understanding DPP-IV Inhibitors

DPP-IV inhibitors, or gliptins, are a pharmacological category of oral antidiabetic agents developed to improve glycemic management in patients diagnosed with type 2 diabetes mellitus (T2DM) (Lamos et al., 2019). The mechanism of action of these medicines involves the inhibition of DPP-IV, an enzyme that plays a crucial role in regulating glucose levels (Bae, 2016).

Mechanism of Action

The primary function of DPP-IV is to facilitate the degradation of incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The production of incretins by the gastrointestinal tract in response to food consumption is a pivotal mechanism in regulating insulin secretion from pancreatic beta cells (Mudaliar & Henry, 2012). Dipeptides located at the N-terminal of these incretin hormones are cleaved off by DPP-IV, resulting in their fast inactivation (Havale & Pal, 2009). This process leads to a reduction in the half-life of these hormones in circulation and a decrease in their ability to induce insulin release (Reed et al., 2021). DPP-IV inhibitors, as their vocabulary implies, impede the enzymatic function of DPP-IV (Domecq et al., 2019). The inhibition process enables GLP-1 and GIP to maintain their activity for extended periods, resulting in an enhanced capacity to promote insulin secretion and limit glucagon release in a way that relies on glucose levels (Sterl et al., 2016). The outcome is enhanced regulation of glucose levels throughout the body, leading to a decreased likelihood of experiencing low blood sugar levels (Figure 2).

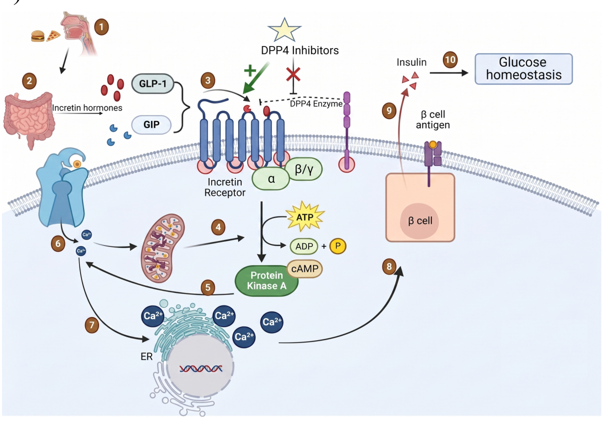

Figure 2: Mechanism of DPP4 Inhibitors in glycemic control

Figure 2 represents the Glycemic control and role of DPP4 inhibitors: 1. After food intake the glucose level inside the body increases.2. The incretin hormones get released ie GIP from K cell and GLP-1 from L-cell. 3.These hormones bound to G-Protein coupled receptor and causes dissociation of α, β, γ. 4. They utilise ATP from mitochondria and activate protein Kinase A. 5. Protein kinase A opens the calcium channel. 6. More amount of calcium enters inside the cytosol. 7. The calcium entry stimulates further release of calcium from rough endoplasmic reticulum. 8. Calcium release stimulates the storage vesicles of β cells. 9. The insulin is released from the pancreatic β cells. 10. Glucose homeostasis is maintained. The binding of incretin hormones to the G-Protein coupled receptor is blocked by DPP-IV enzyme. The DPP4 inhibitors blocks the enzymatic activity and enhances GIP and GLP-1 binding to the receptor and enhance the maintenance of glycemic levels.

Clinical Efficacy of DPP-IV Inhibitors

DPP-IV inhibitors benefit the therapeutic options for managing T2DM. Several agents within this class have been developed and approved for clinical use, including sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin. The effectiveness of these pharmaceuticals in reducing blood glucose levels has been proven as monotherapy and in combination with other antidiabetic medications (N. et al., 2018). One notable benefit of DPP-IV inhibitors is their capacity to maintain weight neutrality or even promote weight management. Unlike certain antidiabetic drugs that can contribute to weight gain, DPP-IV inhibitors do not influence body weight considerably (Gallwitz, 2019a). This characteristic renders them particularly appealing to those who have a higher body weight and are obese. DPP-IV inhibitors are typically associated with a favorable safety profile. When utilized as monotherapy, these medications have a minimal likelihood of hypoglycemia, mainly attributable to their mode of action that is contingent upon glucose levels (Ridge, 2018). On the other hand, it is worth noting that certain alternative antidiabetic medications, such as sulfonylureas, have the potential to induce hypoglycemia, a condition of low blood sugar levels, which poses considerable apprehension for a substantial number of patients (Anderson, 2018).

Furthermore, DPP-IV inhibitors possess a comparatively lower propensity for pharmacological interactions, mitigating the likelihood of untoward effects when co-administered with other pharmaceutical agents (Buzea et al., 2022). The administration of these substances through the oral route not only improves their convenience but also promotes patient compliance. The effectiveness and safety of DPP-IV inhibitors have been well-established by many clinical trials and research (Buse et al., 2020). For example, a meta-analysis conducted by researchers and published in the Journal of Diabetes Research in 2018 analyzed several randomized controlled trials. The findings of this study indicated that the use of DPP-IV inhibitors resulted in a substantial reduction in HbA1c levels, but the risk of hypoglycemia did not show a significant increase (Shen et al., 2018). A systematic review and meta-analysis published in the Journal of Clinical Endocrinology & Metabolism (2016) underscored the weight-neutral impact of DPP-IV inhibitors, rendering them a viable option for individuals with type 2 diabetes mellitus (T2DM) (Inzucchi & Matthews, 2017).

Potential Implications Beyond Glucose Control

Glycemic control is the primary goal of treating type 2 diabetes mellitus (T2DM) using DPP-IV inhibitors. However, emerging studies have shown the existence of possible ramifications extending beyond their core therapeutic function (Kristin, 2016). The considerations mentioned above have generated curiosity regarding examining the broader ramifications of DPP-IV inhibitors.

Cardiovascular Benefits: Several studies have suggested that DPP-IV inhibitors may have cardiovascular advantages. An illustration of this may be seen in the TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), as reported in the New England Journal of Medicine (2015), whereby sitagliptin did not exhibit an elevated likelihood of serious adverse cardiovascular events. This outcome serves to reinforce the safety of sitagliptin (Green et al., 2013).

Renoprotective Effects: According to a study published in Diabetes Care in 2016, DPP-IV inhibitors might exhibit renoprotective properties by reducing albuminuria and decelerating diabetic nephropathy development (MacIsaac et al., 2017). The fundamental processes are currently under investigation.

Anti-Inflammatory Properties: Data suggests that DPP-IV inhibitors may have anti-inflammatory activities. The possible therapeutic benefits of inhibiting DPP-4 include reducing inflammation and cytokine production, which may benefit those suffering from chronic inflammatory disorders like rheumatoid arthritis (Meurot et al., 2022).

Neuroprotection: Recent evidence indicates that DPP-IV inhibitors may possess neuroprotective properties in the context of neurodegenerative conditions such as Alzheimer's disease. The investigation of these putative neuroprotective effects is now a topic of ongoing study (Angelopoulou & Piperi, 2018).

Combination Therapy: DPP-IV inhibitors are frequently employed in conjunction with several other antidiabetic medications, such as metformin, sulfonylureas, and thiazolidinediones, to augment the management of blood glucose levels (Stoian et al., 2020). The integration of several medication classes offers a diverse strategy for the management of T2DM (Artasensi et al., 2020).

CONCLUSION

A thorough knowledge about DPP-IV enzyme and its inhibitors is crucial to throw the limelight on its therapeutic potential and its role in human health. Hence the article explored into the structure, function, and regulation of DPP-IV, emphasizing its numerous roles in health and illness including metabolic regulation, immunology, cancer, cardiovascular disease and wound healing. It also covered the DPP-IV inhibitors and their mechanism in regulating glycemic index and their clinical efficacy.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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