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SARS-CoV-2 and diabetes: A potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19

Zemene Demelash Kifle [a,*], Alem Endeshaw Woldeyohanin [b], Chilot Abiyu Demeke [c]

[a] Department of Pharmacology, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia
[b] Department of Social Pharmacy, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia
[c] Department of Pharmaceutics, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

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ABSTRACT

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 and has become an urgent economic and health challenge. Dipeptidyl peptidase 4 (DPP4), also mentioned as a cluster of differentiation 26 (CD26) is a serine exopeptidase found in two arrangements: a soluble form (sDPP-4) and a plasma membrane-bound form. Because other coronaviruses enter the cells by binding to DPP-4, it has been speculated that DPP-4 inhibitors may exert activity against COVID-19. Therefore, this review aimed to summarize the potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in diabetic patients diagnosed with COVID-19. To include different studies, publications related to Dipeptidyl peptidase-4 inhibitor use and clinical outcomes from COVID-19 were searched from the databases such as Web of Science, PubMed, Medline, Elsevier, Google Scholar, and SCOPUS, via English key terms. A direct engrossment of DPP4 in COVID-19 needs to be elucidated, there is also evidence confirming that DPP4 inhibitors exert anti-fibrotic and modulate inflammation activity. Thus, the use of DPP-4 inhibitors could reduce mortality due to COVID-19 or improve the progression of COVID-19; this evidence may support the management of diabetic patients diagnosed with COVID-19; however more well-designed investigation is urgently required.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 represents a global health threat [1]. It has spread worldwide, as of September 2021, more than 220,655,863 patients are infected and about 4,567,602 deaths were reported due to COVID-19 [2]. Male gender and older age are the two features that have been linked to worse outcomes [3,4]. Although diabetes mellitus (DM) may not be linked to increased risk of infection, it may converse an increased risk for worse progression and prognosis [5,6]. Nearly 2/3 of severely ill patients have at least one comorbidity, usually cardiometabolic diseases, with DM covering 17% of cases [4].

Diabetic patients have a higher risk of acute respiratory distress syndrome, mortality from the COVID19, intensive care unit admission, and severe disease [7,8]. Potential pathogenetic associations between COVID-19 and DM comprise the hyperglycemia-mediated dysregulated immune system, viral proliferation, and altered renin-angiotensin-aldosterone system [7–9]. Moreover, patients with DM are at high risk of severe COVID-19 due to elevated expression of Dipeptidyl Peptidase-4 and angiotensin II converting enzyme-2 mediating infection [10]. Similarly, Patients with DM are thought to have raised pro-inflammatory cytokine levels including tumor necrosis factor-α, interleukin-6, and interleukin-1 [11].

Metformin can constrain the inflammatory response that may contribute to mortality via a mechanism like vascular damage and cytokine storm [12]. In addition to metformin, one of the antidiabetic medications which are frequently used by diabetic patients is the dipeptidyl peptidase-4 inhibitor. This medication has been suggested to benefit in decreasing the mortality and severity from SARS–CoV-2 infection due to its capability to block the host CD26 receptor and modulate the DPP4/CD26 activity, consequently restricting SARS–CoV-2 way to enter T cells [13].

Dipeptidyl peptidase-4 inhibitor is also supposed to have an activity on the enhancement of Glucagon-Like Peptide-1 anti-inflammatory activity, downregulation of macrophages activity/function, and reduction of cytokines overproduction, thus can progress the poor outcomes patients with COVID-19 [10,13]. This review aimed to summarize the potential therapeutic effect of dipeptidyl peptidase 4 inhibitors in

* Corresponding author.
E-mail address: zeme2010@gmail.com (Z.D. Kifle).

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diabetic patients diagnosed with COVID-19.

2. Diabetes as a promoter of mortality and severity in COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 and has become an urgent economic and health challenge because of its pandemic magnitudes [14,15]. In the last two decades other two beta coronaviruses busted, namely MERS)-CoV and SARS-CoV, yet without such epidemic influence. Likewise, to former influenza infections, there is rising evidence that DM is a vital risk factor for the mortality and severity of COVID-19 [3,16,17].

A study revealed that diabetes mellitus and cardiovascular disease are the most dominant cardiometabolic comorbidities in hospitalized COVID-19 infected patients [18]. A cohort study conducted in Europe showed that arterial hypertension, chronic heart disease, and DM are the most common comorbidities in hospitalized patients with COVID-19. Whereas hypertension, obesity, and DM were the most frequent comorbidities in the intensive care unit [19,20]. Moreover, findings revealed that obesity may be associated with increased COVID19 severity [21,22], even in younger patients [23]. Being cardiovascular diseases the main cause of morbidity and mortality in patients with DM, it is not amazing that besides being comorbidities, DM, obesity, and cardiovascular diseases have been reported as risk factors for severity in COVID-19 in numerous studies [24,25].

A study conducted previously revealed that previous cardiovascular comorbidities displayed five-fold greater mortality risk [26]. As the epidemiological study showed that COVID-19 particularly affecting elder patients where diabetes, cardiovascular diseases, obesity, and DM are common comorbidities, it is under argument whether these comorbidities, particularly DM can increase the risk of infection or only the severity [27,28].

3. Cardiovascular effects of sDPP4 upregulation

DPP4/CD26 is a serine protease cleaving an extensive range of substrates such as the gastric inhibitory peptide, cytokines, growth factors, and incretin hormones glucagon-like peptide 1, [29]. DPP4 is existed as a soluble form (sDPP4) or as a membrane-bound form that sustains its enzymatic activity [29]. In the context of diabetes mellitus and obesity, both liver and AT have been suggested as pertinent sources of sDPP4 in humans, though the key source remains under discussion. sDPP4 was identified as a novel adipose-derived factor [30], whose circulating levels are enriched in visceral fat from insulin-resistant and obese patients and relate with BMI [31]. While sDPP4 levels and plasma activity have been linked to fibrosis, NAFLD, fat content, and liver apoptosis [32,33].

DPP4 can endorse systemic and local inflammation by its immunomodulatory effect. Therefore, DPP4 activates cytokine production, T cell activation, and proliferation [34], or through the interaction with immune partners on antigen-presenting cells as manose-6 phosphate receptor, caveolin-1, CD45, or adenosine deaminase [29,35]. DPP4 expression is greater on blood T lymphocytes from DM patients and related to glycated hemoglobin and insulin resistance [36]. sDPP4 treatment enhanced IL-6 secretion and LPS-induced tumor necrosis factor-a in activated monocytes. In addition to its upregulation in obesity and DM, DPP4 expression is higher in senescent cells [37].

A study conducted *In vivo* model revealed that exogenous administration of sDPP4 rise monocyte migration. Fascinatingly, upregulation of DPP4 in diabetic animals and obese have shown immune responses dysregulation [29,33]. DPP4 substrates with cardiovascular impact are upregulated in DM and/or obesity as well as in COVID-19 such as BNP and CXCL5/RANTES [38,39]. Indeed, high BNP levels were positively associated with the occurrence of cardiovascular mortality and events in HIV/AIDS patients and were proposed as a pointer of patient's condition deterioration from mild to severe prognosis [40].

DPP4 is known to interact with extracellular matrix proteins, contributing to both tissue remodeling and cell migration. Through binding to fibronectin, DPP4 can endorse T cell helper accumulation and migration in areas with rising extracellular matrix proteins like damaged blood vessels [41]. DPP4 also interrelates with fibroblast activation protein-a/seprase resulting in invasion and migration of endothelial cells into collagen matrices [42]. Furthermore, stromal cell-derived factor-alpha is also a substrate of DPP4, and inhibition of DPP4 has been detected to rise stromal cell-derived factor-alpha/CXCR4-induced mobilization of endothelial cells [41]. Through its communication with ADA, DPP4 activates plasminogen-2 resulting in increased plasmin levels which pay to the activation of matrix metalloproteinase-4 and degradation of extracellular matrix proteins, which enables diapedesis and immune cells migration [29,43]. Currently, plasmin among other proteases may cleave a new furin site in the spike protein of COVID-19, leading to an increase in severity and infectivity. This high plasmin may pay to the hyperflbrionolysis leading to increased D-dimer in critically ill patients [44]. Notably, in addition to its immunomodulatory activities, sDPP4 can have a direct injurious effect on the vascular wall. sDPP4 directly increased inflammation and human smooth muscle cell proliferation through NF-kB activation leading to upregulation of pro-inflammatory cytokines like IL-6 and IL-8, and monocyte chemoattractant protein-1, via a novel mechanism facilitated by the activation of the protease activated receptor-2 [45]. Moreover, protease activated receptor-2 stimulation persuaded by sDPP-4 activated endothelial dysfunction in mesenteric micro vessels via thromboxane A2 release facilitated by the thromboxane A2 receptor and cyclooxygenase activation [46].

Therefore, DPP4 expression may contribute to the diabetes mellitus-related severity of COVID-19. Moreover, because of its vascular effects, sDPP4 arises as a likely contributor to associated acute respiratory distress syndrome severity via inducing bronchoconstriction and inflammation.

4. Dipeptidyl peptidase-4, dipeptidyl peptidase-4 inhibitors, and COVID-19

DPP-4 also mentioned as a cluster of differentiation 26 (CD26) is a serine exopeptidase found in two arrangements: a soluble form (sDPP-4) and a plasma membrane-bound form (mDPP-4, containing a type two transmembrane homodimeric glycoprotein). The soluble form preserves its peptidase (enzymatic) activity and is supposed to be out from the membrane into the circulation. DPP-4/CD26 is expressed unanimously in numerous tissues and cells such as intestine, endothelia, lung, liver, immune cells (activated B cells, myeloid cells, activated natural killer cells, and T cells), and kidney [47].

DPP-4 has been recognized as an efficient receptor for the spike protein of the MERS-CoV facilitating the virus entry into the host cells [48]. DPP-4 inhibitors like gliptins have been extensively used as antidiabetic agents for the management of type II DM and have been confirmed in improving blood glucose levels through suppressing glucagon secretion and enhancing endogenous insulin secretion and preventing the DPP-4-mediated inactivation and cleavage of incretin hormones [49]. DPP-4 inhibitors include saxagliptin, linagliptin, alogliptin, vildagliptin, and sitagliptin [50]. Both SARS-CoV-2 and SARS-CoV use ACE2 as the main receptor for viral entry into host cells [51]. Though, bioinformatics methods joining protein-docking based on crystal structures, computational model-based selective docking, and human-virus protein interaction prediction suggest DPP-4 as a potential candidate binding target of the receptor-binding S1domain of the COVID-19 spike glycoprotein. Moreover, the crucial binding residues of DPP-4 are similar to those that are bound to the spike protein of MERS-CoV [52,53].

As DPP-4 inhibitors are expressed ubiquitously in numerous tissues and cells other than the respiratory tract and lung, they may consequently contribute to direct COVID-19-mediated damage of such cells and tissues. Therefore, DPP-4 inhibition may play a key role to counter

the DPP-4-mediated COVID-19 virulence and hijacking and to progress clinical outcomes of SARS-CoV-2 by affecting the interaction between target host cells and SARS-CoV-2 [13,54,55]. Though, the main glucose-independent mechanism which is responsible for beneficial activities of DPP-4 inhibition in COVID-19 includes the antifibrotic, anti-inflammatory, and immunomodulatory properties exerted by this class of medications, which may denote an effective therapeutic tool to halt or prevent the progression toward the cytokine storm and hyper-inflammatory state related to the most severe COVID-19 cases [1,56].

Several findings revealed that DPP-4/CD26 modifies both adaptive and innate immune responses [47,57]. DPP-4/CD26 is highly upregulated upon T-cell activation, while it is expressed only on a fraction of resting T-cells [47]. DPP-4/CD26 on T-cell surface persuades co-stimulatory activities on T-cell stimulation, leading to the promoted synthesis of pro-inflammatory cytokines, Th1, TNF-α, IL-6, and IFN-γ [58]. CD26-mediated co-stimulation of $CD8^+$ T cells produces a cytotoxic activity mainly through TNF-α, IFN-γ, Fas ligand, and granzyme B [59]. A study reported by Bengsch et al. revealed that human Th17 cells producing type 17 cytokines like IL-22, IL-17, and TNF showed the maximum levels of enzymatically active DPP-4/CD26 when compared to regulatory T cells, Th1, and Th2 [60]. DPP-4 inhibition has been revealed to constrain the release of IL-6, IL-8, and TNF-α; to reduce lipopolysaccharide-induced lung damage in murine models of ARDS through human lung microvascular endothelial cells [61].

A study conducted by Soare et al. showed that inhibition of DPP4-knockout mice and DPP-4 promoted regression of bleomycin-induced dermal thickness in murine models of systemic sclerosis, were less vulnerable to bleomycin-induced pulmonary fibrosis and dermal [56]. Recent findings revealed that the use of DPP-4 inhibitors in patients with COVID-19 and DM at the time of hospital admission was linked with improved clinical outcomes, a greater number of hospital discharges, lower need for noninvasive mechanical ventilation, and decreased mortality [62,63]. According to a study done by Solerte et al., 338 following hospitalized diabetic patients with COVID-19 (169 were on sitagliptin, while 169 were on a standard of care). Treatment with Sitagliptin was linked with improvement in clinical outcomes, decreased mortality at the time of hospitalization, and a higher number of hospital discharges when compared to patients on standard of care [62]. In a similar study done by Mirani et al., out of 387 hospitalized patients infected with COVID-19; 90 of them (23.3%) had diabetes mellitus. In patients with DM, the use of DPP-4 inhibitors was independently and significantly related to a reduced risk of mortality [63]. An observational study reported that the use of DPP-4 inhibitors is linked with a noticeable reduction of mortality in diabetic patients with COVID-19 [64]. This study suggests that DM patients with COVID-19 taking DPP-4 inhibitors may display lower COVID-19-related end-organ complications and pneumonia. Furthermore, it has been shown that DPP-4 inhibitors may provide cardioprotective activities through several mechanisms including dyslipidemia, oxidative stress, immunity dysfunction, apoptosis, adipose tissue dysfunction, insulin resistance, and antiapoptotic activity of these medications in the vasculature and heart [65].

Several studies have revealed that DPP-4 inhibitors can prevent the development and progression of atherosclerosis, improve endothelial function, and facilitate wound healing through modulating monocyte/macrophage-mediated responses, attenuating vascular oxidative stress, and reducing neutrophil recruitment and activity [57]. Therefore, Du et al. have recently proposed DPP-4 inhibition as a potential therapeutic strategy aimed to alleviate cardiovascular injury (including arrhythmia, acute coronary syndrome, and heart failure) caused either directly by SARS-CoV-2 or indirectly by the COVID-19-induced cytokine storm [66].

Numerous studies revealed that sitagliptin have anti-inflammatory activity in diabetic patients, leading to rise the expression of an anti-inflammatory cytokine (IL-10) and reduced expression of various markers of pro-inflammatory cytokines, cell adhesion molecules, and low-grade inflammation, such as E-selectin IL-6, serum amyloid A-low-density lipoprotein complex, IL-18, secreted phospholipase-A2, TNF-α, soluble intercellular adhesion molecule-1, and C-reactive protein [67–69]. A Phase II clinical trial revealed that the combination of sitagliptin and a standard immunosuppressive regimen of sirolimus and tacrolimus caused a low occurrence of acute graft-versus-host disease [70]. Therefore, the immunomodulatory and anti-inflammatory activities of DPP-4 inhibitors may have an advantage in the management or prevention of cytokine storm in patients with COVID-19. The protective activity of DPP-4 inhibitors against COVID-19 may relies on the hypothesis of inhibition of DPP-4, which may result in a significant increment in circulating levels of the soluble form of DPP-4 [71,72]. The consequent abundance of soluble form of DPP-4 can provide a binding sites for COVID-19, therefore limiting or preventing the attachment of the virus to the membrane-bound DPP-4 on target host cells, such as endothelial cells, pneumocytes, or other cells pertinent for viral replication and spread [71].

5. Dipeptidyl peptidase-4 as a therapeutic target in diabetic patients with COVID-19

5.1. Gliptins

DPP4 inhibitors (gliptins) are antidiabetic medications that control glucose homeostasis via inhibition of dipeptidyl peptidase-4 enzymatic activity. Dipeptidyl peptidase-4 inactivates and cleaves the incretin hormones GIP and GLP-1, which are responsible for the release of postprandial insulin (60–70%); hence, DPP4 inhibitors extend the half-life of incretins. In addition, its effect on incretins, DPP4 inhibitors (gliptins) has been suggested to provide other off-target activities such as cardiovascular effects. There is a continuing argument concerning dipeptidyl peptidase-4 inhibition as a potential therapeutic approach to prevent and manage cardiovascular diseases in DM and/or obese patients. Prominently, gliptins are favored as add-on therapy in patients with DM streaming with previous cardiovascular or chronic kidney disease [73].

Cardiovascular safety of gliptins has been reported in numerous cardiovascular outcome trials (NCT00790205; NCT01107886; EXAMINE, TECOS, CARMELINA, NCT00968708; NCT01897532; SAVOR TIMI 53,). Gliptins have shown a significant decrement of glycated hemoglobin levels, neutral influence on body weight, and no risk of hypoglycemic episodes, which are vital factors related to reduced cardiovascular mortality and risk [74]. Furthermore, DPP4 inhibitors have shown positive activities over surrogate vascular endpoints, such as lipemia, blood pressure, and endothelial function [75]. It has been revealed that a combination of gliptin and metformin can significantly reduced the risk of nonfatal cardiovascular events, cardiovascular mortality, and all-cause mortality when compared with other antidiabetic medications like sulfonylureas [76].

The indirect cardioprotective activities of gliptins are improved by increased bioavailability of substrates of DPP4 (GLP-1). Diabetic patients managed with sitagliptin exhibited high SDF-1a plasma levels leading to augmented endothelial progenitor cells, which have a significant role in vascular repair [77]. In vitro study revealed that SDF-1a was capable of increasing blood flow in a model of peripheral artery disease [78]. Similarly, an increase in BNP improved the regulation of the vasodilatory responses and natriuresis [79]. *Ex vivo* endothelial dysfunction, as well as hVSMC inflammation and proliferation exerted by sDPP4, were equally prevented by the clinically and experimental available linagliptin and DPP4i K579, respectively [45,46]. This suggests that these medications could have cardiovascular benefit in addition to controlling glucose homeostasis.

In the *in-vivo* model, gliptins have shown protective activities. Streptozotocin-induced diabetic rats treated with vildagliptin were showed decreased oxidative stress and expression of plasminogen activator inhibitor type-1 and ICAM-1 [80]. In db/db mice linagliptin

enhanced cardiovascular dysfunction by decreasing the upregulation of collagen-1 and collagen-3 and reducing the stimulation of the Nlrp3/ASC inflammasome [81]. Likewise, sitagliptin also enhanced cardiovascular function in mice [82]. Anti-oxidant activity of DPP4 inhibitors has been also revealed under acute inflammation in the *in-vivo* model of LPS persuaded sepsis.

In diabetic patients, treatment with sitagliptin decreased the molecular markers of inflammation as IL-6 and CRP in mononuclear cells [67], as well as circulating levels of IL-1b, IL-6, TNF-a, CRP, and intracellular adhesion molecules [69]. Sitagliptin also enhanced the flow-mediated vasodilation effect in adult diabetic patients [83]. Prominently, sitaglipitin has shown a cardio protective effect in chronic kidney disease diabetic patients [84]. Gliptins improve endothelial function through their anti-oxidant, potentially protective effects on the vascular system, and anti-inflammatory [85], which are important in fighting SARS-CoV-2. Furthermore, a randomized clinical trial revealed that treatment with gliptin didn't raise the risk of infections in diabetic patients [86]. In addition to providing potential cardiovascular protection, gliptins also play a key role to confine COVID-19 binding to the host cells. Vildagliptin, saxagliptin, or Sitagliptin can't inhibit MERS-CoV entrees to Vero cells [87].

All DPP4 inhibitors (gliptins) are competitive reversible inhibitors of dipeptidyl peptidase-4 enzymatic activity [88]. According to the subsites within the DPP4 molecule they occupy, gliptins can be grouped into three categories. Class one includes peptidomimetic DPP4 inhibitor with the greatest basic binding to DPP4 like saxagliptin and vildagliptin; class two inhibitors include linagliptin and alogliptin; and class three inhibitors include teneligliptin and sitagliptin exhibit an increased interacting point. The higher the interacting points the more the inhibitory activity [89]. Fascinatingly, class one and two gliptins (alogiptin, saxagliptin, and linagliptin) can bind near to a residue (Tyr547) in a zone beyond DPP4 pockets S1 and S2 called S1′ subsite [89]. The uracil ring of linagliptin and alogliptin results in conformational alteration on DPP4 S1' subsite impeding its enzymatic effect (Nabeno et al., 2013). Thus, this type of xhantine-based non-peptidomimetic gliptins may weaken COVID-19 binding to one of its favored sites in dipeptidyl peptidase-4. Furthermore, linagliptin and vildagliptin have been prophesied to bind ACE2 with similar or even higher binding capacity than they have for dipeptidyl peptidase-4 [90].

The pharmacodynamic and pharmacokinetic profiles of DPP4 inhibitors allow that dipeptidyl peptidase-4 enzymatic activity in circulation and tissues is not completely blocked [91]. Both genetic deletion of DPP4 and DPP4 inhibition with des-fluro sitagliptin in mice didn't alter T-cell-dependent immune responses [92]. Saxagliptin, vildagliptin, and sitagliptin didn't change the innate immune response triggered by Toll-like receptor activation in terms of co-stimulation, secretion, and T cell migration and proliferation both in mice *in-vivo* and human cells *in-vitro* [93].

A previous study revealed that DPP4 inhibitors are not linked with increased risk for respiratory infections they may raise the risk of nasopharyngitis and urinary tract infection [94]. A similar study showed that long-term use of sitagliptin in diabetic patients has not increased the risk of infection [95]. Another finding also reported that there was no association between the risk of respiratory tract infections and glucose-lowering therapies among diabetic patients [96]. But, the potential induction of cough in asthma [97], angioedema [98] or leucopenia [99] by DPP4 inhibitors epitomizes potential drawbacks to their use as a therapeutic agent in patients with COVID-19 [100]. However, further investigation will help to know if DPP4 inhibitors can affect immune homeostasis, T cell development, and infection risk in diabetic patients (Table 1) [47].

5.2. *sDPP4 as soluble decoy factor*

A study conducted in VERO cells showed that exogenous administration of sDPP4 repressed MERS-CoV infection [87]. Thus, SARS-CoV-2 can bind to DPP4, administration of exogenous sDPP4 as a decoy factor will compute with the virus to bind with an endogenous DPP4. sDPP4 load benefit may depend on the blockade of detrimental pathways worsening/affecting immune responses and on virus trapping and prominently, to prevent SARS-CoV-2 effects on the vasculature. Hence, exogenous administration of sDPP4 via *in-vitro* model was shown a

Table 1
Summarized effects of sDPP4-targeted agents reported in preclinical and clinical research.

Agents	Preclinical data		Previous clinical trials	COVID-19
	Cells	Animal models		Ongoing clinical trials
Gliptins	• Block MERS-CoV infection in macrophages [110]. • Prevention of sDPP4-induced hVSMC proliferation and inflammation [45].	• Prevention of sDPP4-induced endothelial dysfunction in mice [46]. • Anti-oxidant effects in STZ-induced diabetic rats and LPS-induced sepsis mouse model, respectively [80,111]. • Reduction of NLRP3/ASC inflammasome activation in db/db mice [81]. • Improved cardiac function in mice [82].	• Decreased risk of non-fatal CV events and CV mortality [76]. • No risk of infection in type 1 and type 2 diabetic patients [86]. • Increased cardio and vasculoprotective substrates [28,78,79]. • Anti-inflammatory effects in type 2 dibatec patients [67,69]. • Improved flow-mediated vasodilation in diabetic patients [83]. • Potential induction of leucopenia, angioedema, cough and asthma [97,98].	• SIDIACO Sitagliptin (NCT04365517) • Linagliptin: NCT04371978, NCT04341935
sDPP4	• Block MERS-CoV infection in Vero cells [87]. • hVSMC proliferation and inflammation [45]. • Pro-inflammatory effects [45,46]. • Inhibition of T-cell activation and proliferation via ADA binding [101].	• Endothelial dysfunction in murine mesenteric microvessels [46]. • Increased monocyte migration in LDLR−/− mice [112].		• Direct truncation of CCL5/RANTES: reduced IL-6 levels and viremia (Iwata et al., 1999; Patterson et al., 2020)
AntiDPP4 vaccine	• Blockade of MERS-CoV infection [107]. • No effects on T-cell proliferation or cytokine production [106].	• Increased GLP-1 in type 1 and type 2 diabetic mice [104,105].		

preventive effect on the formation of endogenous DPP4/CD26-ADA complex in human macrophages/dendritic cells leading to inhibited proliferation and activation of T-cells [101]. Disruption of CCL5-CCR5/RANTES axis with the anti-CCR5 antibody leronlimab decreased plasma viral load and IL-6 plasma levels in patients diagnosed with COVID-19 [102]. It has been suggested that sDPP4 can directly shorten RANTES/CCL5 obstructing its union to CCR5 [103], thus sDPP4 can show the same activity as leronlimab management, resulting in a reduced cytokine storm and an improved immune response. In patients with diabetes mellitus, it was reported that the plasma concentration of sDPP4 is significantly increased [31], therefore, the possible risk-benefit of exogenous administration of sDPP4 as decoy factor should be judiciously explored (Table 1).

5.3. Anti-DPP4 vaccine

Anti-DPP4 vaccination is another therapeutic modality confirmed to control plasma DPP4 activity through the *in-vitro* model. The anti-DPP4 vaccine didn't cause any side effect on the immune-mediated attack towards DPP4expressing cells nor immune cell activation. Moreover, it showed comparable activity to gliptin treatment regarding GLP-1 plasma levels and glycemia control in animal models of both type I and type II DM [104,105]. In a study conducted on *in-vitro* on human CD26-positive lymphocytes, a humanized IgG1 monoclonal antibody with high affinity for CD26 was assessed, which showed no effect on cytokine production and T-cell proliferation [106]. Fascinatingly, humanized IgG1 monoclonal antibodies also repressed MERS-CoV infection [107]. Though, it has been argued that *in-vivo* administration of anti-DPP4 antibodies can counteract plasma sDPP4 prior to impede virus entry and coate cellular DPP4. In this condition, intranasal administration of anti-DPP4 antibodies or sDPP4 has been a reasonable solution to overwhelmed such effects (Xia et al., 2014). In contrast, CD26/DPP4-related signaling was effectively obstructed via the soluble fusion protein Caveolin-Ig, which confirmed extra immune-suppressive activity [108]. Tissue factor pathway inhibitor is a biological inhibitor of DPP4. Furthermore, because of its anticoagulant activity (Mast, 2016), tissue-factor pathway blocker may be seen as a positive feature in the situation of COVID-19 management (Table 1) [109].

6. Conclusion

DPP-4 inhibitors are a class of oral antidiabetic agents extensively used for the management of Type II diabetes mellitus; and have been proposed as a potential binding target of the receptor-binding S1 domain of the COVID-19 spike glycoprotein. DPP-4 inhibition could have the potential to block the interaction between target host cells and SARS-CoV-2; and current findings suggest that DPP-4 inhibitors display anti-fibrotic properties, anti-inflammatory, and immunomodulatory in addition to their confirmed antidiabetic activity. The use of DPP-4 inhibitors could reduce mortality due to COVID-19 or improve the progression of COVID-19; this evidence may support the management of diabetic patients diagnosed with COVID-19; however more well-designed investigation is promptly required.

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CRediT authorship contribution statement

Zemene Demelash Kifle: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Roles/. **Alem Endeshaw Woldeyohanin:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Roles/. **Chilot Abiyu Demeke:** Software, Supervision, Validation, Visualization, Roles/.

Declaration of competing interest

The authors declares that they have no competing interests.

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