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REVIEW

Classical and alternative receptors for SARS-CoV-2 therapeutic strategy

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Abstract

Understanding the molecules that are essential for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) entry can provide insights into viral infection and dissemination. Recently, it has been identified from several studies that angiotensin-converting enzyme 2 receptor and transmembrane serine protease 2 are the main entry molecules for the SARS-CoV-2, which produced the pandemic of Covid-19. However, additional evidence showed several other viral receptors and cellular proteases that are also important in facilitating viral entry and transmission in the target cells. In this review, we summarized the types of SARS-CoV-2 entry molecules and discussed their crucial roles for virus binding, protein priming and fusion to the cellular membrane important for SARS-CoV-2 infection.

KEYWORDS
ACE2, Covid-19, entry molecule, SARS-CoV-2, TMPRSS2

1 | INTRODUCTION

Covid-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is classified within the *Betacoronavirus* genus, which also contains SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[1] Covid-19 was declared a pandemic by the World Health Organization (WHO) in March 2020. People infected with SARS-CoV-2 develop Covid-19 and have shown several symptoms, including fever, dry cough, tiredness, headache, abdominal pain and diarrhoea.[2,3] The loss of smell, or anosmia, has been reported as one of the early symptoms among persons infected with SARS-CoV-2.[4] Also, Covid-19 patients were diagnosed with pneumonia and having a ground glass opaque appearance on the lungs through a computed tomography (CT) scan.[5,6] Progression of Covid-19 disease in infected people may eventually advance to multiple organ failure and even lead to death.[7,8]

1.1 | SARS-CoV-2 entry molecules

SARS-CoV-2 receptor and cellular protease in the host body are key entry molecules that have been recognised to play an essential role in the transmission of SARS-CoV-2 infection leading to Covid-19 disease. SARS-CoV-2 spike protein consists of two subunits, which are S1 (receptor-binding subunit) and S2 (fusion subunit). The S1 subunit is responsible for binding the receptor via its receptor-binding domain, while the S2 subunit is responsible for viral fusion to the

Abbreviations: ACE2, angiotensin-converting enzyme 2; AGTR2, angiotensin II receptor type 2; Ang 1–7, angiotensin 1–7; Ang II, angiotensin II; ANPEP, alanyl aminopeptidase; CatB/L, Cathepsin B and L; CoV, coronavirus; Covid-19, coronavirus disease-2019; CT, computed tomography; CUB, for complement C1r/C1s, Uegf, Bmp1; DPP4, dipeptidyl peptidase 4; HEK, human embryonic kidney; HR, heptad repeat; MAM, meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu; ENPEP, glutamyl aminopeptidase; MERS-CoV, Middle East respiratory syndrome coronavirus; NRP, neuropilin; RAS, renin–angiotensin system; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; S protein, spike protein; TMPRSS2, transmembrane serine protease 2; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

target cell membrane.[9,10] Proteolytic cleavage catalysed by endogenous protease is required to facilitate the viral fusion to the cellular membrane and enter the target cells.[11] This review will discuss the classical and several alternative receptors for SARS-CoV-2, together with their cellular proteases implicated in Covid-19 disease.

2 | RECEPTORS FOR SARS-CoV-2 ENTRY

2.1 | Angiotensin-converting enzyme 2

Angiotensin-converting enzyme 2 (ACE2) plays a primary role in the conversion of angiotensin II (Ang II) to angiotensin$_{1-7}$ (Ang 1–7).[12] ACE2 is also vital in regulating cardiac function and various organs through the renin–angiotensin system (RAS).[13] Though ACE2 shares some homology with ACE and has 61% similarity in the amino acids, ACE2 is not inhibited by ACE inhibitors.[12,14] In Covid-19, ACE2 plays a key role in SARS-CoV-2 entry and its infection. ACE2 serves as a primary receptor for the SARS-CoV-2 spike protein (S protein) to bind and enter human cells.[15,16] The receptor-binding domain of the virus S protein binds to ACE2 causes SARS-CoV-2 to undergo endocytosis and exposes it to endosomal proteases leading to viral infection in the host.[17–19] Zhou et al.[20] revealed that HeLa cells with ACE2 expression are susceptible to infection with SARS-CoV-2 compared to cells without ACE2 expression.

Recent sequencing data on normal human tissues by Li et al.[21] showed that ACE2 is highly expressed in the small intestine, testis, kidneys, heart and thyroid, followed by medium expression of ACE2 in the lungs, large intestine, bladder, liver and adrenal glands. ACE2 showed the lowest expression in the blood, spleen, bone marrow and brain. The findings indicate that expression of ACE2 in various organs may explain SARS-CoV-2 infection out with the lungs.[21] Notably, in the lungs, SARS-CoV-2 has been reported to infect mainly type II pneumocytes,[22] demonstrated by a post-mortem study on the lung tissue histology of Covid-19 patients, which revealed cellular fibromyxoid exudates with a bilateral distribution of alveolar damage.[23] Zhao et al.[24] also demonstrated in their RNA expression study using normal human lung samples, where 83% of the ACE2 receptor is expressed in the type II pneumocytes. Interestingly, ACE2-expressing type II pneumocytes appeared to be involved in the viral life cycle, viral process, viral assembly and viral replication via enrichment analysis indicating their roles for transmission in humans.[24] A recent study by Lukassen et al.[25] showed that apart from lung tissues, ACE2 is also expressed mainly in the subsegmental bronchial branches, particularly in the transient secretory cells.

SARS-CoV-2 infection will lead to the downregulation of ACE2 in the infected cells as the virus interacts with ACE2-expressing cells in the lung epithelium and other organ tissues. Upon SARS-CoV-2 infection, ACE2 can be shed from the lung tissue to the bronchial space, thus, reducing the ACE2 level of the infected cells. Meanwhile, the ACE2 shed in the bronchial space is still capable of converting Ang II to Ang (1–7).[7] The ACE2 remains capable of binding to the SARS-CoV-2 in the bronchial space, but it will enter the cells because the ACE2 shed is no longer attached to the epithelial cell. Also, it is reported that the ACE2 shed has an unknown physiological function.[26] The question of whether this shedding behaviour of ACE2 can prevent SARS-CoV-2 infection or can predict the prognosis of disease progression[27] is still to be answered, and further study is needed.

However, ACE2 as the entry receptor is not limited to SARS-CoV-2 since it is also the receptor for SARS-CoV infection.[28] The tendency for SARS-CoV-2 and SARS-CoV to bind the ACE2 receptor may be due to both viruses sharing 76.5% sequence homology.[23] Moreover, Xu et al.[23] also reported that the receptor-binding domain in both SARS-CoV-2 and SARS-CoV S proteins has a similar structure. Nevertheless, ACE2 has better affinity with up to 20-fold higher binding to the SARS-CoV-2 S protein than the SARS-CoV S protein.[10] A crystallography study by Shang et al.[29] reported that the SARS-CoV-2 has a broader linking interface with ACE2 as compared to the SARS-CoV. ACE2 is known to serve as a binding receptor, and although ACE2 is present in various organs, it does not indicate that the SARS-CoV-2 may enter through all different organs that have the ACE2 receptor. The entry of SARS-CoV-2 to target cells that mainly occurs via endocytosis may rely on the viral S protein binding to the ACE2 receptor and the presence of cellular proteases to cleave the viral S protein.[30]

2.2 | CD147

Another receptor for SARS-CoV-2 infection has been discovered through an in-depth study. CD147, a receptor on host cells,[31] is a transmembrane glycoprotein,[32] and is commonly known as basic immunoglobulin (Basigin) or extracellular matrix metalloproteinase inducer (EMMPRIN).[33] Distinct from ACE2 expression, CD147 is highly expressed in pathological tissues such as in tumour tissues[34,35] and inflamed tissues,[36,37] suggesting little cross-reactivity with normal tissue.[33] Besides, in contrast to ACE2, CD147 is greatly expressed in the brain cell lines and brain tissues than in the lung cells.[38] CD147 is highly expressed on human embryonic kidney (HEK)293 cell lines and facilitated the entry of SARS-CoV into the HEK293 cells. However, the application of CD147 antagonistic peptide-9 (AP-9) successfully blocked SARS-CoV infection in HEK293 cells.[32] Since both SARS-CoV and SARS-CoV-2 are acknowledged to have a similar characteristic,[23] more studies have been performed to determine the functional role of CD147 as an entry receptor for SARS-CoV-2.[32–37] Recently, a study by Wang et al.[33] demonstrated significant inhibition of SARS-CoV-2 from invading Vero E6 cells upon meplazumab application, an inhibitor for CD147. Wang et al.[33] also revealed the interaction and binding between CD147 and SARS-CoV-2 S protein via surface plasmon resonance assay, ELISA test and co-immunoprecipitation assay, thus identifying an alternative receptor for the entry of SARS-CoV-2 to host cells. In accordance with this finding on CD147, a phase II clinical trial (NCT04275245) is currently ongoing in China, targeting the entry of SARS-CoV-2 by blocking the CD147 receptor with

meplazumab. Hence, the CD147 receptor may act as a potential therapeutic target in Covid-19 patients.

When CD147 was initially isolated from the human lung carcinoma (LX-1 cell line), CD147 was found to induce matrix metalloproteinases (MMP) production that is responsible for fibrosis in tumour progression.[39,40] It is reported that CD147 was also presented in non-tumour tissues such as in the alveolar macrophages and type II pneumocytes in the lungs, which indicates its role may be related to the MMP production.[41] Guillot et al.[41] described that CD147 was highly expressed in the fibrosis area of lung parenchyma compared to the normal lung area, indicating the association between CD147 and fibrosis. Moreover, it is demonstrated that the inhibition of CD147 by the anti-CD147 antibody prevented TGF-B1-induced myofibroblasts formation.[31] Indeed, recent clinical findings suggested that lung fibrosis and fibrous stripes are among the major complications from SARS-CoV-2 infection.[42–44] Hence, targeting the CD147 receptor may also be advantageous to prevent the burden of lung fibrosis in Covid-19 patients. At the same time, additional study is necessary to approve whether CD147 acts as a novel new receptor, as a co-receptor with ACE2, or as an alternative secondary receptor.

2.3 | Neuropilin-1

Neuropilin (NRP) may become another docking receptor to facilitate SARS-CoV-2 entry. It has four domains consisting of the N-terminal CUB (for complement C1r/C1s, Uegf, Bmp1) domain, coagulation factor domain, MAM (meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu) domain and transmembrane domain.[45] Neuropilin consists of two family members, NRP1 and NRP2. NRP1 is a transmembrane protein of relative molecular mass (Mr) 130,000 and acts as a receptor that binds to furin-cleaved substrates. It acts as a regulator of the vascular endothelial growth factor (VEGF)-induced angiogenesis cellular signalling cascades, sprouting, and controlling cell migration in vessel remodelling and angiogenesis.[46–48] However, its signalling is associated with cancer as it could promote angiogenesis and increased vascular permeability, causing oedema.[49] Its overexpression is associated with poor tumour prognosis such as in the gastrointestinal (GI) tract, prostate, lung, ovary, and gliomas, osteosarcomas, and melanomas.[50]

NRP1 is not only expressed in the respiratory epithelium but also the olfactory epithelium. Particularly, NRP1 is highly expressed in endothelial cells, excitatory neurons and nasal cavity epithelial cells[51,52]. Increased expression has been identified in biological samples from Covid-19 patients and suspected to aid viral invasion.[53] Moreover, Daly et al.[54] revealed that NRP1 was capable of binding the S1 protein of SARS-CoV-2 through the mechanism of canonical C-end rule, and NRP1 was shown to be a host factor for SARS-CoV-2 in cell culture study. Positive NRP1 cells in the olfactory epithelium and endothelial cells of the olfactory bulb were infected by the virus.[53] The entry of SARS-COV-2 into the nervous system is likely via the interaction of virus S protein and the receptor located in the olfactory system.[55] Specifically, the binding occurs through the b1/b2 domain on the NRP1 receptor through a polybasic amino acid sequence (682RRAR685).[56] Currently, the potential monoclonal blocking antibody was being studied to block the extracellular b1/b2 domain of NRP1.[53]

2.4 | Dipeptidyl peptidase 4

Dipeptidyl peptidase 4 (DPP4), also known as CD26, is an ecto-peptidase present on the surface membrane of different types of cells[57] such as in the immune system, kidneys, lungs, smooth muscle, liver and capillaries.[57,58] DDP4 plays a role in various physiological processes and immune-system-related diseases.[59] The expression of DDP4 and its relation to injuries in the human respiratory tract from coronavirus infection have been shown previously in MERS-CoV infection.[60]

A study to determine virus infectivity in HeLa cells showed that the SARS-CoV-2 did not bind to the DPP4 receptor.[20] However, a binding conformation between DPP4/CD26 and SARS-CoV-2 spike glycoprotein has recently been reported, so it is suggested that both MERS-CoV and SARS-CoV-2 may have shared the mode of entry through DPP4.[61] Also, Qi et al.[62] showed DDP4 as a potential receptor for SARS-CoV-2 infection as it has a similar expression pattern with the ACE2 receptor. A study by Venkatakrishnan et al.[63] agreed with the data from Qi et al.,[62] where they depicted that DPP4 has a high similarity of expression profiles to ACE2 receptor. A study on the inhibition of DPP4 activity using a mouse model depicted lower T-cell counts that reduced airway inflammation.[64] As some of the Covid-19 patients have developed inflammatory tissue damage in their airways,[65] future studies targeting on DPP4 activity are required that may be beneficial to reduce the burden of inflammatory reaction in Covid-19 patients.

2.5 | Other possible receptors for SARS-CoV-2

There are few studies about alanyl aminopeptidase (ANPEP), glutamyl aminopeptidase (ENPEP) and angiotensin II receptor type 2 (AGTR2) in relation to SARS-CoV-2. ANPEP is a known entry receptor for several viruses in the family *Coronaviridae*, including human CoV-229E, porcine epidemic diarrhoea virus, feline CoV, canine CoV, infectious bronchitis virus and transmissible gastroenteritis virus.[62,66] ANPEP is highly expressed in several organs, including the ileum, colon, rectum, kidneys, skin and liver.[62] However, in the conjunctiva, Leonardi et al.[67] demonstrated low-level expression of ANPEP, which is similar to ACE2 receptor expression in the conjunctiva. Like DPP4, a recent study by Qi et al.[62] revealed a significant association of ANPEP with ACE2 receptor, indicating that ANPEP may act as an entry receptor for SARS-CoV-2. ANPEP is also reported to be a neutrophil-specific gene, suggesting the possibility of SARS-CoV-2 infection of neutrophils.[68]

ENPEP is a mammalian type II integral membrane zinc-containing endopeptidase from the aminopeptidase family.[62] ENPEP plays an

important role in regulating blood pressure and remodelling blood vessels via the RAS catabolic pathway.[69] Recently, Qi et al.[62] identified ENPEP as a new possible entry receptor for SARS-CoV-2 as ENPEP has no history of acting as a receptor for human coronaviruses. They showed that the expression pattern of ENPEP was similar to the ACE2 receptor expression. The real reason behind the similar expression patterns needs further investigation to confirm the role of ENPEP. However, it may be due to the same types of cells infected by different human coronaviruses, which could lead to a similar expression.

AGTR2, a G-protein coupled receptor, is postulated as another receptor for SARS-CoV-2.[70] Cui et al.[70] demonstrated high and specific expression of AGTR2 in the lung, indicating the high possibility of AGTR2 acting as an entry receptor for SARS-CoV-2 infection, mainly through the respiratory system. However, AGTR2 expression is lower in the cornea and conjunctiva.[67] Cui et al.[70] found out AGTR2 has a greater binding affinity towards SARS-CoV-2 S protein compared to ACE2 through simulation of 3D structure-based protein–protein interaction and revealed that AGTR2 was capable of interacting with ACE2. Hence, further additional studies are required to confirm the significance role of AGTR2 as an entry receptor, or as a co-receptor that acts together with ACE2 or possibly with other entry receptors for SARS-CoV-2. Table 1 summarizes the receptors for SARS-CoV-2 entry with their site of expression.

3 | PROTEASES FOR SARS-CoV-2 ENTRY

3.1 | Transmembrane serine protease 2

Transmembrane Serine Protease 2 (TMPRSS2) is known as the cellular protease that the SARS-CoV-2 virus utilizes to facilitate virus entry into the target host cells.[16] Apart from the cell receptor, the SARS-CoV-2 entry requires viral S protein cleavage and activation of the host cell protease, which is the TMPRSS2 to mediate viral infection.[16] The S2 subunit of the viral S protein consists of two heptad repeat (HR) regions (HR1 and HR2) and a fusion peptide region.[18,19] Within the endosome, the S1 subunit is cleaved, exposing the fusion peptide, thus allowing the viral fusion to the cellular membrane as the S2 region folds to pull together the HR1 and HR2 regions.[18,19] Then, proceed to membrane fusion and viral entry into the host.[25,71] Several parts in the human respiratory system, including the lungs and subsegmental bronchial branches, show TMPRSS2 expression.[25] Analysis of single-nucleus RNA sequencing on normal human lungs revealed that TMPRSS2 expression has more affinity in the type II pneumocytes, similar to ACE2 expression in the lungs.[25,72] Other than type II pneumocytes, several sites show co-expression of TMPRSS2 and ACE2, such as the transient secretory cells in the subsegmental bronchial branches,[25] enterocytes in the small intestine,[22] heart, liver and kidney.[73] Thus, the positive co-expression sites of both TMPRSS2 and ACE2 may be vulnerable for the SARS-COV-2 entry. Nevertheless, Liu et al.[74] demonstrated only a little expression of TMPRSS2 in the heart, which may indicate low heart vulnerability towards the SARS-COV-2 infection. Consequently, the findings by Liu et al.[74] was in agreement with the previous pathological studies on Covid-19 cases where no substantial damage was found on heart tissue, apart from just a few infiltrations of inflammatory cells[75] and no sign of viral particles in cardiac myocytes.[76]

The essential role of TMPRSS2 as an entry molecule was reported by Hoffmann et al.,[16] in which application of camostat mesylate, a TMPRSS2 blocker, showed partial inhibition of SARS-CoV-2 into CaCo-2 cells. Moreover, a previous study on SARS-CoV using TMPRSS2^{-} knockout mice revealed a reduction in viral loads and body weight compared to control wild-type mice, indicating the crucial role of TMPRSS2 in facilitating viral entry to the target cells.[77] A recent study by Milne et al.[78] demonstrated the association between smokers and increased expression of *TMPRSS2* gene, and *ACE2* expression in the human lungs. Moreover, Wu et al.[79] showed a strong association between exposure to air pollution and Covid-19 mortality. These findings depict that smoking and exposure to air pollution may cause several comorbidities that can worsen lung

TABLE 1 Receptors for SARS-CoV-2 entry with their site of expression, and possible injuries and complications

Receptor	Site of expression	Possible injuries and complications
ACE2	High expression in the small intestine, testis, kidneys, heart, and thyroid. Medium expression in the lungs, large intestine, bladder, liver, and adrenal glands[21]	Cellular fibromyxoid exudates with a bilateral distribution of alveolar damage[23]
CD147	High expression in tumour tissues and inflamed tissues[34–37]	Fibrosis[39–41]
NRP1	The respiratory epithelium, olfactory epithelium, endothelial cells, excitatory neurons, and nasal cavity epithelial cells[51,52]	Angiogenesis in cancer[46–48] and increase vascular permeability, causing edema[49]
DPP4	The kidneys, lungs, smooth muscle, liver, and capillaries[57,58]	Inflammation[64]
ANPEP	High expression in the ileum, colon, rectum, kidneys, skin, and liver[62]	Infection of neutrophils[68]
ENPEP	Expression pattern similar to ACE2 expression[62]	Irregular blood pressure[69]
AGTR2	High expression in the lungs[70]	Possible lung-related complications[70]

Abbreviations: ACE2, angiotensin-converting enzyme 2 receptor; AGTR2, angiotensin II receptor type 2; ANPEP, alanyl aminopeptidase; DPP4, dipeptidyl peptidase 4; ENPEP, glutamyl aminopeptidase; NRP1, neuropilin-1.

injury, leading to severe Covid-19 cases, particularly in Covid-19 patients having a respiratory disease.

3.2 | Cathepsin B and L

Cathepsin B and L (CatB/L) are known as main lysosomal proteases, responsible for monitoring the function of lysosomes.[80] Apart from lysosomes, cathepsins are also commonly found in endosomes.[81] Cathepsin expression and activity have been commonly associated with aging neurons.[82] A study on the expression pattern of cathepsin L in the adult heart revealed about 28.6% of the whole heart expressed cathepsin L.[74] Besides, Liu et al.[74] discovered that cathepsin L expression level in the heart is considerably higher than in the lungs. Since TMPRSS2 has a little expression in the heart as compared to the lungs,[74] the high expression level of cathepsin L in the heart could become one of the factors that contribute to the few cases with dominant cardiac involvement in Covid-19 patients.[83,84] Further study is required to determine the association.

In SARS-CoV infection, the virus can use CatB/L apart from TMPRSS2 which is required for S protein priming.[17,85] Nevertheless, the activity of CatB/L is dispensable as compared to the activity of TMPRSS2 in facilitating viral entry into the targeted cells and transmission within the infected host.[77,86] A recent study by Hoffmann et al.[16] identified the role of CatB/L for SARS-CoV-2 S protein priming. Interestingly, SARS-CoV-2 showed dependence on CatB/L for viral entry into the TMPRSS2$^{(-)}$ Vero cells upon inhibition by camostat mesylate, the protease inhibitor for TMPRSS2. However, 293T cells with TMPRSS2 expression facilitated SARS-CoV-2 entry to the cells, although they are inhibited by E-64d, the CatB/L blocker. Moreover, Hoffmann et al.[16] also revealed significant inhibition of SARS-CoV-2 entry into TMPRSS2^{+} CaCo-2 and TMPRSS2^{+} Vero cells upon the addition of camostat mesylate and E-64d, which is the inhibitor of CatB/L. Hence, Hoffmann et al.[16] indicate that SARS-CoV-2 is capable of utilizing both CatB/L and TMPRSS2 cellular proteases for the viral S protein priming.

A recent finding by Ou et al.[30] revealed cathepsin L rather than cathepsin B as a critical protease for SARS-CoV-2 entry to HEK 293/hACE2 cells. Ou et al.[30] showed no changes to virus entry upon application of cathepsin B inhibitor (CA-074) to HEK293/hACE2 cells, as compared to more than 76% inhibition towards SARS-CoV-2 entry to the cells after application of cathepsin L inhibitor (SID 26681509). However, a study by Jaimes et al.[87] found the opposite results where cathepsin L showed more proteolytic cleavage towards SARS-CoV rather than SARS-CoV-2 as compared to cathepsin B that did not cleave the SARS-CoV but was active towards SARS-CoV-2. Nevertheless, whether SARS-CoV-2 follows the same SARS-CoV trait for S protein priming by TMPRSS2 rather than by CatB/L to allow viral entry, or SARS-CoV-2 may use CatB/L as an alternative of viral infectivity route remain to be answered through further investigations.

3.3 | Furin

Studies to identify the ultimate cellular protease to cleave SARS-CoV-2 S protein are ongoing. In vitro study by Hoffmann et al.[16] showed that SARS-CoV-2 entry was not entirely prohibited even after TMPRSS2 and CatB/L blockage. This finding indicates that there is another protease that may facilitate in SARS-CoV-2 S protein priming. A recent paper by Monkemuller et al.[88] stated that furin, an endogenous serine protease, plays a role in cleaving the virus S protein to facilitate virus attachment to the ACE2 receptor and cell membrane before viral entry into the host cell. A phylogenetic study by Xia et al.[11] reported the presence of a furin-like cleavage site (FCS) at the SARS-CoV-2 S1/S2 subunit, which was not present in other types of SARS-related viruses. The ability of furin to cleave the S protein at the FCS site is postulated to be the reason behind the higher binding affinity between SARS-CoV-2 and ACE2 receptor.[89] However, this hypothesis requires confirmation.

A recent investigation by Hoffmann et al.[16] implicated furin in the SARS-CoV-2 S proteolytic process at the S1/S2 site by using furin inhibitor, decanoyl-RVKR-CMK. Interestingly, the proteolytic process of SARS-CoV-2 S was also inhibited, indicating the need for furin to cleave the S protein at the S1/S2 site. It is reported that furin is commonly distributed in the small intestine, and can enhance the pathogenicity of some bacteria and viruses.[88] Since some papers have described gastrointestinal symptoms such as diarrhoea, nausea and vomiting in patients with Covid-19[89,90], the small intestine may serve as one of the viral entry sites for SARS-CoV-2, facilitated by furin.

Moreover, the increase of transmission rates from humans to humans is postulated due to the role of furin, which can be secreted and act to cleave the S protein even in the target cells that do not express furin.[25] Again, this hypothesis requires further investigation. Shang et al.[91] revealed a remarkable role of furin preactivation towards facilitating SARS-COV-2 entry to some target cells that have lower TMPRSS2 and/or cathepsin proteases expression. Since protease activation is essential to allow viral structural conformation for membrane fusion, Shang et al.[91] showed that by furin preactivation, the SARS-COV-2 might no longer be dependent on target cells, especially the cells that have low proteases such as TMPRSS2 and/or cathepsin, increasing viral entry to the human body.

3.4 | Trypsin

Trypsin has been reported as one of the proteases that may act as the SARS-CoV-2 entry molecule.[30] Trypsin, a serine endopeptidase, is highly expressed in respiratory cells and gastrointestinal cells, particularly in the small intestine.[81] A study by Bertram et al.[92] showed that human airway trypsin-like protease is capable of cleaving and activating SARS-CoV S protein, which might be responsible for viral spread in humans. Recently, Ou et al.[30] showed the role of trypsin in activating SARS-CoV-2 S protein to allow viral fusion to HEK293T cell lines. Nevertheless, the SARS-CoV-2 S protein is still capable of being activated even with the blockage of

TABLE 2 Proteases for SARS-CoV-2 entry and their site of expression

Protease	Site of expression	Reference
TMPRSS2	Type II pneumocytes, subsegmental bronchial branches, enterocytes in the small intestine, heart, liver, kidney, and neurons.	22,25,73
CatB/L	High expression in the heart	74
Furin	Small intestine	88
Trypsin	Respiratory cells and gastrointestinal cells, particularly in the small intestine.	81

Abbreviations: CatB/L, Cathepsin B and L; TMPRSS2, transmembrane serine protease 2.

trypsin. This finding indicates that other possible proteases in HEK293T cells may activate the SARS-CoV-2 S protein. There is still a lack of evidence to support trypsin as the SARS-CoV-2 entry molecule to this date so more studies are required. A summary of the proteases for SARS-CoV-2 entry and their site of expression is presented in Table 2.

4 | THERAPEUTIC STRATEGY TARGETING THE ENTRY MOLECULES

Currently, dexamethasone and remdesivir, two examples of drugs, are licensed to treat hospitalised Covid-19 patients based on randomised clinical trials.[93,94] However, many studies are still ongoing to search for effective therapeutic strategies to treat and prevent Covid-19 disease. As SARS-CoV-2 S protein facilitates receptor binding and membrane fusion, targeting the receptor or disrupting the viral fusion may act as an essential strategy to control the viral infection. Specifically, inhibition of the interaction between the SARS-CoV-2 receptor and viral S protein may be particularly useful. Previously in SARS-CoV infection, recombinant ACE2 (rhACE2) was identified to block the virus from binding to the receptor and appeared as a therapeutic potential for SARS,[95] which could also be applied for Covid-19 treatment. However, a recent clinical trial proposed in China on rhACE2 as a treatment for Covid-19 patients has been withdrawn (NCT04287686). Another clinical trial on soluble rhACE2 (APN01) for Covid-19 treatment proposed by Apeiron (NCT04335136) is planned to be developed in Europe. It is expected that the soluble rhACE2 would block SARS-CoV-2 infection and alleviate tissue injury.

Besides, targeting cellular proteases that play a vital role in viral fusion can also be included in the therapeutic strategy for Covid-19. A recent study by Hoffman et al.[71] showed that camostat mesylate, a serine protease inhibitor of TMPRSS2, can partly prevent the entry of SARS-CoV-2-S. However, they revealed the combination of E64d, a cathepsin B/L protease inhibitor, and camostat mesylate appeared to completely block SARS-CoV-2 S-mediated viral entry into 293T cells.[71] Nevertheless, the SARS-CoV-2 has been reported to bind to other receptors and is not limited to ACE2. Moreover, the availability of several cellular proteases to aid in membrane fusion for viral entry is another crucial factor to be considered in a therapeutic approach for Covid-19. This therapeutic strategy targeting the entry molecules may help prevent SARS-CoV-2 infection in the early phase. However, the strategy may not be entirely effective in the late phase of the disease due to the possibility of cytokine storm-induced acute respiratory distress syndrome, which in some cases may contribute to patient mortality. Therefore, a better pharmacological approach that may consider the classical and alternative viral receptors and proteases are suggested to be developed as a countermeasure for SARS-CoV-2 infection.

5 | CONCLUSION

The reason for the immense human-to-human transmission of SARS-COV-2 cases compared to SARS-COV or MERS-COV remains to be answered. Hence, possible factors related to viral entry could be due to varieties of potential receptors on the cell surface, diverse cellular proteases and the host factor itself that may influence the virus to enter the human body. While the development of effective treatment targeted to viral entry molecules is still ongoing and urgently needed, current efforts to reduce viral transmission such as physical distancing and wearing masks should be consistently practised in our daily lives.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors scoped and constructed the literature search. Nurul Farhana Jufri, Farah Wahida Ibrahim and Sayyidi Hamzi Abdul Raub screened the abstract and full text. Siti Fathiah Masre wrote the manuscript. All authors reviewed and contributed the writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as there is no new data were analysed in this study.

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