


REVIEW

COVID-19 and renin angiotensin aldosterone system: Pathogenesis and therapy

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Abstract

Aims: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE2 component of the renin-angiotensin aldosterone system (RAAS) and infects the human cells. The aims of the present review were to look at the role and alteration of the RAAS components in SARS-CoV-2 infection, therapeutic approaches, and clinical trials in this field.

Methods: We surveyed the literature (PubMed, Web of Science, and Scopus) till August 18, 2021, and 59 published papers regarding the components of the RAAS and their role and alterations in SARS-CoV-2 infection along with various COVID-19 therapies based on the RAAS components were included in the study.

Results: ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor inhibitors are agents that significantly enhance the ACE2 and Ang-(1-7) levels, which can be suggestive for their role as therapeutics against SARS-CoV-2 infection. Beta-adrenergic blockers, which negatively regulate renin release from juxtaglomerular cells, and vitamin D, as a regulator of the RAAS and renin expression, are proposed therapeutics in the treatment of COVID-19. Some antihyperglycemic agents could be potentially protective against COVID-19-induced lung injury. Also, the inhibition of the Janus kinase/signal transducer and activator of the transcription pathway as a potential treatment for COVID-19 has been suggested. Finally, resveratrol, an antioxidant that can suppress Ang II, has been suggested as an adjunct to other therapies.

Conclusion: Regarding the suggested potential therapies for COVID-19, there are many clinical trials whose results might change the treatment strategies of SARS-CoV-2 infection. So, the results of well-organized clinical trials on the efficacy and safety of the mentioned agents in the treatment of COVID-19 will be useful in the management and therapy of the disease.

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KEYWORDS

ACE2, antihyperglycemic drugs, COVID-19, Janus kinase inhibitors, RAAS inhibitors, SARS-CoV-2

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for coronavirus disease 2019 (COVID-19) through binding to angiotensin-converting enzyme 2 (ACE2), a counter regulator of renin-angiotensin aldosterone system (RAAS), enters the cells and infects them.¹ ACE2 was discovered 20 years ago and has 60% homology with angiotensin-converting enzyme 1 (ACE1), but its active site is different from ACE, so ACE inhibitors do not inhibit the ACE2 activity.² ACE2 acts as a receptor for the viral spike protein of SARS-CoV-2.³

The RAAS plays an important role in glucose metabolism and the regulation of blood pressure, electrolytes, and fluid homeostasis. The RAAS pathway includes renin, angiotensinogen (AGT), ACE/ACE1, ACE2, angiotensin II type 1 receptor (AT1R), and angiotensin II type 2 receptor (AT2R) components. The RAAS components act in two opposite axes: the classical axis composed ACE, angiotensin (Ang) II, and AT1R involved in body fluid homeostasis. Also, this axis triggers vasoconstriction and cardiac hypertrophy and produces reactive oxygen species.⁴ The alternative axis consists of ACE2, Ang-(1-7), and the Mas receptor (Mas R), which counter-regulates the classical RAAS axis and has vasodilatory, anti-inflammatory, and anti-thrombotic effects and inhibits the cell growth and reactive oxygen species production.^{4,5} All these components are present in the local or tissue RAAS, which is regulated independently of the systemic RAAS that is found in kidneys, heart, lungs, blood vessels, and many other tissues.⁶ The renin, an aspartyl protease, catalyzes the degradation of AGT to the inactive decapeptide of Ang I. The ACE converts the Ang I to the active vasoconstrictor octapeptide of Ang II. This peptide increases the aldosterone secretion, elevates blood pressure, and inhibits renin secretion.⁷ Angiotensin-(1-9), Ang-(1-7), Ang III, and Ang IV are other Ang I cleavage products. An alternate pathway of Ang I metabolism is through ACE2, which removes a single C-terminal Leu residue from Ang I in order to generate Ang-(1-9) that might amplify in the presence of ACE inhibitors.⁸ The ACE2, a membrane-bound aminopeptidase, degrades the Ang I into Ang-(1-9) and Ang II to Ang-(1-7) peptides. The Ang-(1-7), a G-protein-coupled receptor, exerts vasodilatory, antiproliferative, and apoptotic functions through binding to Mas R.⁷ The role of Mas as a receptor of Ang-(1-7) was elucidated using radioligand-binding studies with Ang II and also Mas-knockout mice studies. Angiotensin-(1-7) counteracts Ang II and accumulates in patients treated with ACE inhibitors (ACEIs) that highlights the possibilities for treating cardiovascular diseases through the agonists for the Ang-(1-7)-Mas axis.⁹ The high expression of ACE homolog, ACE2, mRNA in the heart and kidneys, as important organs involved in blood pressure homeostasis, might indicate its role in the cardiovascular and renal function regulation.¹⁰

The SARS-CoV-2, similar to SARS-CoV, uses the ACE2 for entering the cells.¹¹ The binding of SARS-CoV-2 to the membrane-bound ACE2 as its functional receptor facilitates the entry of the virus into the cells.⁴ Four main structural proteins, spike (S), envelope (E), nucleocapsid (N), and membrane (M), have been detected in SARS-CoV-2. The S proteins, which are large membrane-linked glycoproteins, have a critical role in viral infection through binding to their receptor, ACE2, on host cells and also by membrane fusion. The affinity between S1 subunit, one of the two subunits of S protein, and host ACE2 receptor determines host susceptibility to SARS-CoV2 infection.¹² The SARS-CoV-2 is attached to the cell surface through binding to ACE2 in a multistep variation of conformational state, and the membrane fusion step is started. After S1 receptor-binding domain binds to ACE2, transmembrane protease/serine subfamily 2 (TMPRSS2) degrades the S2 domain to facilitate membrane fusion. It seems that SARS-CoV-2 cell entry leads to downregulation of membrane-bound ACE2, which results in the lung injury and vasoconstriction. Moreover, other membrane proteins are necessary for SARS-CoV-2 entry into the cells by priming and activation of the S protein.⁴ Therefore, ACE2, which is found in the human lower respiratory tract, acts as a cell receptor for SARS-CoV. The ACE2 is also expressed in the mucosa of the oral cavity, with higher expression in tongue than other oral regions.¹¹ Hence, the ACE2-expressing cells in oral tissues could be the possible routes of COVID-19 entry.¹¹ In addition, ACE2 is highly expressed in type II epithelial cells where its tissue activity is higher than plasma.¹³ Furthermore, the activity of the RAAS and ACE2 is high in the lungs.¹³ Moreover, other organs with high ACE2-expressing cells are at high risk for COVID-19 infection. The high affinity of SARS-CoV-2 to ACE2 could explain the greater infectivity of this virus compared to other human CoVs.⁴

Age, diabetes mellitus, hypertension, chronic respiratory diseases, chronic kidney diseases, cardiovascular diseases, and cancers are risk factors for COVID-19 and its severity. The most affected population with COVID-19 is individuals with age group of 50 to 60 years. A positive association between severity and aging has been observed, which seems to be due to the higher prevalence of preexisting comorbidities, and lifespan physiological oscillation of the RAAS components. In the process of aging, the RAAS axes equilibrium is modified, and upregulation of ACE/Ang II/AT1R and increased plasma renin activity occurs. The presence of comorbidities such as hypertension and diabetes was associated with unfavorable outcomes in patients with COVID-19. These comorbidities are closely correlated with highly increased activation of ACE/Ang II/AT1R axis. Therefore, severe forms of COVID-19 can result from the previous history of the RAAS imbalance, which favors the inflammatory state. However, the ACE2 expression might be crucial in the prognosis of the disease due to utilizing RAAS inhibitors by several diabetic and/or hypertensive patients for

management of the classical axis upregulation.⁴ The prognosis of COVID-19 is also dependent on the sex, as the ACE2 expression in females is higher than males.¹³ Regarding age- and sex-dependent expression of ACE2, there are many aspects that need to be elucidated.

At present, there is no approved antiviral drug for the treatment of COVID-19. However, in addition to approaches working on antiviral therapy, others have focused on the components of the RAAS. In the present review, we have looked at the role and alteration of the RAAS components including ACE2 and Ang-(1-7) in SARS-CoV-2 infection, therapeutic approaches, and clinical trials in this field. Also, we described therapies and clinical trials using ACEIs, angiotensin receptor blockers (ARBs), and renin inhibitors in SARS-CoV-2 infection and COVID-19 outcomes. Furthermore, the therapies and clinical trials designed based on the crosstalk of the RAAS with kallikrein/kinin pathway, hyaluronic acid (HA) degradation, neprilysin (NEP) activity, glucose homeostasis, and Janus-activated kinase (JAK) pathway and the role of antioxidant of resveratrol in relation to the Ang II are discussed.

2 | METHODS

In this review, we surveyed the literature (PubMed, Web of Science, and Scopus) till August 18, 2021, and 59 published papers discussed the RAAS pathway and its cross talk with the kallikrein/kinin pathway, HA degradation, and NEP activity, and their role and alterations in SARS-CoV-2 infection were included in the present review. Also, papers and clinical trials, according to "ClinicalTrials.gov" website related to various COVID-19 therapies based on recombinant human ACE2 (rhACE2), Ang-(1-7), ACEI, ARBs, renin inhibitors, antihyperglycemic drugs, JAK inhibitors, and the antioxidant of resveratrol in relation to the modulation of the RAAS components have included in the present study.

3 | RESULTS

3.1 | ACE2 and SARS-CoV-2 infection

In a study on the treatment of seven patients with COVID-19 pneumonia in China, the role of ACE2 in SARS-CoV-2 infection was confirmed using intravenous transplantation of mesenchymal stem cells (MSCs) that were negative for both ACE2 and the type II transmembrane serine proteases TMPRSS and free from COVID-19 infection. The pulmonary function and the symptoms of patients were significantly improved 2 days after MSCs transplantation.¹⁴ Some studies suggested that metallopeptidase domain 17 (ADAM17) is essential for cellular entry of SARS-CoV through binding SARS-S to ACE2 that triggers processing of ACE2 by ADAM17 and facilitates ACE2 shedding into the extracellular space, and increases SARS-CoV uptake into cells.^{15,16} However, Heurich et al using in vitro studies indicated that proteolysis ACE2 by TMPRSS2 and HAT augmented the SARS-S-driven entry to the cells with highly increased viral uptake. Also, their study demonstrated a competition between TMPRSS2 and ADAM17 for ACE2 cleavage, although only processing of ACE2 by TMPRSS2

enhanced entry of the virus to the cells.¹⁷ There are evidences of the significant hypomethylation of the promoter region of the ACE2 gene on the X chromosome and its overexpression in peripheral blood mononuclear cells of patients with lupus erythematosus.¹⁸

The rhACE2 or adenoviral (Ad)-ACE2 has been used as a therapeutic agent in animal diseases models and also has been used and well-tolerated in a clinical trial including 44 patients with acute respiratory distress syndrome (ARDS).¹⁹ Animal studies indicated that the rhACE2 acts as an important negative regulator of Ang II and inhibits adverse myocardial remodeling.²⁰ The ACE2 activity in the circulation is significantly increased by rhACE2, which is accompanied by effective decline of Ang II levels and increased production of Ang-(1-7) from Ang II. Injection of a chimeric fusion of rACE2-Fc (immunoglobulin fragment Fc segment) increased the overall Ang II-conversion activities in blood up to 100 times and recovered induced hypertension in mice. Also, rACE2-Fc decreased kidney and cardiac fibrosis.²¹ Verma et al suggested a combination therapy by applying GapmeR technology with rhACE2 in the treatment of COVID-19 patients. GapmeR is an antisense single-stranded DNA molecule that is designed to a specific target and binds to the SARS-CoV-2 RNA, and then, the produced DNA-RNA hybrid is degraded by intracellular RNAase-H. On the other hand, rhACE2 blocks entering the virus to the host cells.²² Moreover, the protective role of soluble ACE (sACE) is justified by the absence of increased risk of SARS-CoV-2 infection in inflammatory bowel disease (IBD) patients because of sACE2 upregulation in the peripheral blood of these patients.²³ In another approach, cyclodextrin (CD)-sACE2 inclusion has been suggested for the treatment of this infection.²⁴ Various compounds of aerosolized sACE2 to be directly inhaled into the lungs, intravenous infusion of sACE2, and ophthalmic and nasal drops made from CD-sACE2 inclusion compounds have been suggested for the treatment of COVID-19.²⁵

Searching the "ClinicalTrials.gov" website until July 14, 2021 has revealed three clinical trials currently underway, evaluating rhACE2 in COVID-19 patients (Table 1).

3.2 | Angiotensin-(1-7)

A modified version of Ang-(1-7) with long-lasting release property, hydroxypropyl- β -cyclodextrin-Ang-(1-7) complex that allows the oral administration of this compound has been suggested as a therapeutic compound in COVID-19. Intravenous infusion of cyclic Ang-(1-7), a more resistant form of Ang-(1-7) to enzymatic hydrolysis, has had long-term vasorelaxant effects in animal studies.²⁴ Six clinical trials related to the evaluation of Ang-(1-7) infusion in patients with COVID-19 are demonstrated in Table 2.

3.3 | ACE inhibitors and angiotensin receptor blockers

ACE inhibitors such as enalapril and lisinopril elevate tissue/plasma ACE2 levels in animal studies. The angiotensin receptor blockers/

TABLE 1 Clinical trials using recombinant ACE2 in the treatment of COVID-19

Study	Registry identifier	Title	Interventions
1	Nct04375046	Recombinant bacterial ACE2 receptors-like enzyme of B38-CAP could be promising COVID-19 infection- and lung injury-preventing drug better than recombinant human ACE2	Recombinant bacterial ACE2 receptors-like enzyme of B38-CAP (RBACE2)
2	Nct04583228	Evaluate the safety, tolerability, pharmacodynamics, pharmacokinetics, and immunogenicity of HLX71 (recombinant human angiotensin-converting enzyme 2-FC)	HLX71
3	NCT04335136	Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19 (APN01-COVID-19)	RhACE2 APN01

TABLE 2 Clinical trials using angiotensin-(1-7) in the treatment of COVID-19

Study	Registry identifier	Title	Interventions
1	NCT04401423	TXA127 for the treatment of severe COVID-19	Intravenous angiotensin-(1-7) (TXA127)
2	NCT04332666	Angiotensin-(1, 7) treatment in COVID-19: the ATCO Trial (ATCO)	Intravenous angiotensin-(1-7) infusion
3	NCT04570501	Angiotensin-(1-7) for the treatment of COVID-19 in hospitalized patients	Intravenous angiotensin-(1-7) infusion
4	NCT04633772	Use of angiotensin-(1-7) in COVID-19	Intravenous supplementation of angiotensin-(1-7)
5	NCT04375124	Treatment of angiotensin peptide (1-7) for COVID-19	Angiotensin-(1-7) derived plasma
6	NCT04605887	Angiotensin 1-7 as a therapy in the treatment of COVID-19	Subcutaneous angiotensin- (1-7)

angiotensin receptor antagonists/sartans (losartan, olmesartan, irbesartan, and telmisartan) increase tissue/plasma or urinary ACE2 levels in animal models and also in hypertensive patients (olmesartan). Furthermore, mineralocorticoid receptor inhibitors (MCRIs)/aldosterone antagonists increase ACE2 activity in patients with heart disease (spironolactone) and in mice (eplerenone).²⁶ There are some molecular models and studies using human tissues and experimental animal models, which investigate the influence of RAAS inhibitors on ACE2 activity. In a molecular model based on studies conducted in both animals and human tissues to examine the effect of pharmacological therapy on the RAAS pathway, a relationship between the RAAS pathway and SARS-CoV infection was found. Moreover, this model demonstrated that treatment with ARBs, sartans, alone or in combination with ACEIs resulted in increased cell membrane ACE2 activity with a higher risk of viral infection. However, treatment with ACEIs alone have had a protective role due to the decreased ACE2 levels on cell membranes and enhanced ACE2 in the plasma. This model was confirmed in a rapidly recovering patient of SARS-CoV-2 infection who had been on long term and overuse of ACEIs.¹² Although ACE2 activity is not inhibited by traditional ACEIs, the use of ACEIs in animal experiments has indicated an increased ACE2 level and activity.¹³ Some animal studies have shown that ACEIs or ARBs increase ACE2 levels.²⁷ Also, blockade of AT1R by losartan has diminished lung damage in mice who had been administered the SARS-CoV-1 glycoprotein spike.²⁸ There are some experiences from China regarding RAAS

inhibitors and COVID-19. In a retrospective review of medical records from hospitalized COVID-19 patients with hypertension, it was observed that the inflammatory response was attenuated in patients who received ACEIs or ARBs therapy, through the inhibition of IL-6 levels, and also there was a lower rate of severe diseases in these cases.²⁹ This study suggested the potential benefit of using ACEIs or ARBs in the improvement of clinical outcomes of COVID-19 patients with hypertension.²⁹ Analysis of COVID-19 cases in China demonstrated that the case fatality rate in patients with comorbidities (cardiovascular diseases, diabetes mellitus, and hypertension) was much higher than those without comorbidities. However, the age as a confounder should be considered in the evaluation of the high fatality rates.³⁰ A large meta-analysis including 28 872 SARS-CoV-2-infected patients taking ACEIs/ARBs indicated the absence of association between the use of ACEIs/ARBs and the severity and mortality of COVID-19. However, taking ACEIs/ARBs in hypertensive patients had beneficial effects leading to 0.67 times less incidence of fatal/critical outcomes compared to those not on ACEIs/ARBs ($P = .01$). Furthermore, being treated with a ACEIs/ARBs was associated with a significantly lower risk of death.³¹ In addition, in a meta-analysis including 25 observational studies, neither ACEIs nor ARBs were associated with incidence of SARS-CoV-2 infection, hospitalization, severe or critical forms of the disease, intensive care unit admission, and SARS-CoV-2-related death.³² Registries of clinical trials related to the RAAS inhibitors are listed in Table 3.³¹

TABLE 3 RAAS inhibitors clinical trials and COVID-19 treatment

Study	Registry identifier	Title	Interventions
1	NCT04340557	Do angiotensin receptor blockers mitigate progression to acute respiratory distress syndrome with SARS-CoV-2 infection	Losartan
2	NCT04643691	Losartan and spironolactone treatment for ICU patients with COVID-19 suffering from ARDS (COVIDANCE)	Losartan + spironolactone
3	NCT04364893	Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors and adverse outcomes in patients with COVID-19	Suspension vs maintenance of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors
4	NCT04322786	The use of angiotensin-converting enzyme inhibitors and incident respiratory infections, are they harmful or protective?	ACE inhibitor
5	NCT04345406	Angiotensin-converting enzyme inhibitors in the treatment of COVID-19	ACEIs: Captopril or enalapril with conventional treatment of alexoquine (chloroquine) for COVID-19
6	NCT04394117	Controlled evaluation of angiotensin receptor blockers for COVID-19 respiratory disease	Angiotensin receptor blockers Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
7	NCT04329195	ACE inhibitors or ARBS discontinuation in context of SARS-CoV-2 pandemic	Continuation of RAS blocker therapy vs discontinuation of RAS blocker therapy
8	NCT04353596	Stopping ACE inhibitors in COVID-19	Stopping or replacing ACE inhibitor, angiotensin receptor blocker
9	NCT04335786	Valsartan for prevention of acute respiratory distress syndrome in hospitalized patients with SARS-CoV-2 (COVID-19) infection disease	Valsartan (Diovan)
10	NCT04335123	Study of open-label losartan in COVID-19	Losartan
11	NCT04328012	COVID MED Trial—Comparison of therapeutics for hospitalized patients infected with COVID-19 (COVIDMED)	Losartan
12	NCT04606563	Host response mediators in coronavirus (COVID-19) infection: is there a protective effect of losartan on outcomes of coronavirus infection? (ARBS CORONA II)	Losartan
13	NCT04447235	Early treatment with ivermectin and losartan for cancer patients with COVID-19 infection (TITAN)	Ivermectin+losartan
14	NCT04312009	Losartan for patients with COVID-19 requiring hospitalization	Losartan
15	NCT04311177	Losartan for patients with COVID-19 not requiring hospitalization	Losartan
16	NCT04351581	Effects of discontinuing renin-angiotensin system inhibitors in patients with and without COVID-19 (RASCOVID-19)	Discontinuation of ACEI/ARB compared to continuation of ACEI/ARB
17	NCT04355936	Telmisartan for treatment of COVID-19 patients	Telmisartan 80 mg twice daily plus standard care
18	NCT04510662	Telmisartan in respiratory failure due to COVID-19 (STAR-COVID)	Telmisartan 40 mg daily plus standard care.
19	NCT04359953	Efficacy of hydroxychloroquine, telmisartan, and azithromycin on the survival of hospitalized elderly patients with COVID-19 (COVID-Aging)	Hydroxychloroquine, azithromycin, telmisartan
20	NCT04360551	Pilot clinical trial of the safety and efficacy of telmisartan for the mitigation of pulmonary and cardiac complications in Covid-19 patients	Telmisartan 40 mg
21	NCT04356495	Trial of COVID-19 outpatient treatment in individuals with risk factors for aggravation (COVERAGEFrance)	Telmisartan and ciclesonide
22	NCT04466241	Combination therapies to reduce carriage of SARS-CoV-2 and improve outcome of COVID-19 in ivory coast: a phase randomized IIb trial (INTENSE-COV)	Lopinavir/ritonavir, telmisartan, atorvastatin

(Continues)

TABLE 3 (Continued)

Study	Registry identifier	Title	Interventions
23	NCT04493359	Switch of renin-angiotensin system inhibitors in patients with COVID-19 (SWITCH-COVID)	Renin-angiotensin system inhibitors switch anti-hypertensive class
24	NCT04508985	The McGill RAAS-COVID-19 Trial (RAAS-COVID)	Temporarily holding the RAAS inhibitor
25	NCT04591210	The COVID-RASi trial (COVID-19)	Angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers
26	NCT04467931	ACEI or ARB and COVID-19 severity and mortality in US Veterans	ACEI/ARB vs non-ACEI/ARB
27	NCT04338009	Elimination or prolongation of ACE inhibitors and ARB in Coronavirus Disease 2019 (REPLACECOVID)	ARB/ACEI
28	NCT04382950	Combination of recombinant bacterial ACE2 receptor-like enzyme of B38-CAP and isotretinoin could be promising treatment for COVID-19 infection- and its inflammatory complications	Intravenous recombinant bacterial ACE2 receptors-like enzyme of B38-CAP + aerosolized 13 cis retinoic acid
29	NCT04578236	Efficacy of aerosol combination therapy of 13 cis retinoic acid and captopril for treating Covid-19 patients via indirect inhibition of transmembrane protease, serine 2 (TMPRSS2)	13 cis retinoic acid + captopril
30	NCT04715763	INvestigating TELmisartin Study (INTEL)	Oral Telmisartan
31	NCT04920838	Early treatment of vulnerable individuals with non-severe SARS-CoV-2 infection (COVERAGE-A)	Telmisartan 20 Mg Oral Tablet and Nitazoxanide and Ciclesonide

3.4 | Renin inhibitors

3.4.1 | Beta-adrenergic blockers

A cohort study from three hospitals of China included 2190 patients with COVID-19 indicated patients who took beta-adrenergic blockers (BB) before hospitalization had significantly reduced dyspnea. Also, elder patients with COVID-19 who took BB prior to hospitalization had improved clinical indices, except for the blood clot biomarker.³³

3.4.2 | Vitamin D

An inverse correlation between blood pressure and the levels of 25(OH)-D has been demonstrated.³⁴ The bronchoalveolar lavage fluid (BAL) gene expression analysis indicated that the vitamin D receptor (VDR) was downregulated and the enzymes that catabolize 1,25(OH) 2-D and its precursor 25(OH)-D were upregulated in COVID-19 patients compared to controls, which might enhance the renin level.³⁵ Table 4 demonstrates 34 clinical trials related to vitamin D3 as a renin inhibitor compound.

3.5 | Kallikrein/kinin pathway and crosstalk with the RAAS

Animal studies indicate that Ang-(1-7) has potentiated the hypotensive effect and the vasodilatory function of BK. It was suggested that Ang-(1-7) might stimulate the BK release through stimulation of AT2R. Moreover, Ang-(1-7) augmented BK by inhibiting ACE and

releasing NO.³⁶ Analysis of gene expression from cells in COVID-19 patients' BAL samples suggested that the BK system is also severely affected. Compared to controls, in these patients, most of the enzymes degrading BK, including ACE, are downregulated, which direct BK1-9 and BK1-8 to the upregulated BKB2 and BKB1 receptors, respectively; this results in BK storm that might be responsible for many of the observed COVID-19 symptoms.³⁵

3.6 | Hyaluronic acid, the RAAS, and BK

Similar to the RAAS and BK systems, the genes encoding HA synthesis and degradation have been severely affected with significant upregulation of the HA synthesis genes (HAS1-3) in the COVID-19 patients' BAL samples. However, the genes involved in the HA degradation have been downregulated in the BAL fluid of COVID-19 patients. An association between HA with pulmonary thrombosis and/or ground-glass opacities has been observed in radiological findings.³⁵ It was found that Ang II increases CD44 expression and hyaluronidase activity.³⁵

3.7 | Nephilysin, the RAAS, and COVID-19

The role of NEP in COVID-19 is controversial. It has been suggested that increased NEP activity might be involved in decreased COVID-19 severity by diminishing Ang II formation and directing Ang I to generate Ang-(1-7). Also, NEP degrades BKs and therefore prevents the activation and recruitment of the inflammatory cells.³⁷ In contrast, it has been demonstrated that sacubitril (NEP inhibitor)/valsartan

TABLE 4 Clinical trials related to vitamin D3

Study	Registry identifier	Title	Interventions
1	NCT04344041	COVID-19 and vitamin D supplementation: a multicenter randomized controlled trial of high-dose vs standard-dose vitamin D3 in high-risk COVID-19 patients (COVITTRIAL)	Cholecalciferol 400 000 IU vs 50 000 IU
2	NCT04407286	Vitamin D testing and treatment for COVID 19	Dietary supplement of 10 000-15 000 IU/day vitamin D3
3	NCT04482673	Vitamin D supplementation in the prevention and mitigation of COVID-19 infection	Daily and bolus vitamin D3
4	NCT04535791	Efficacy of vitamin d supplementation to prevent the risk of acquiring COVID-19 in healthcare workers	4000 IU daily vitamin D3
5	NCT04502667	Efficacy of vitamin d treatment in pediatric patients hospitalized by COVID-19	1000/and or 2000 IU daily vitamin D3
6	NCT04449718	Vitamin D supplementation in patients with COVID-19	200 000 IU on hospital admission
7	NCT04363840	The lead COVID-19 trial: low-risk, early aspirin and vitamin D to reduce COVID-19 hospitalizations	Aspirin/ aspirin-vitamin D3
8	NCT04483635	Prevention of COVID-19 with oral vitamin D supplemental therapy in essential healthcare teams	10 000 IU vitamin D3 daily and then weekly
9	NCT04536298	Vitamin D and COVID-19 trial	Daily 3200 IU vitamin D3
10	NCT04385940	Vitamin D and COVID-19 management	Weekly 50 000 IU vitamin D3
11	NCT04641195	Vitamin D and zinc supplementation for improving treatment outcomes among COVID-19 patients in India	Vitamin D3 bolus-zinc gluconate
12	NCT04636086	Effect of vitamin D on hospitalized adults with COVID-19 infection	25 000 IU vitamin D3 daily and then weekly
13	NCT04525820	High-dose vitamin D substitution in patients with COVID-19: a randomized controlled, multicenter study	Single high dose of vitamin D3 (140'000 IU)
14	NCT04334005	Vitamin D on prevention and treatment of COVID-19	Single dose of 25 000 IU of vitamin D3
15	NCT04351490	Impact of zinc and Vitamin D3 supplementation on the survival of aged patients infected with COVID-19	Daily 2000 IU vitamin D3-zinc gluconate
16	NCT04579640	Trial of vitamin D to reduce risk and severity of COVID-19 and other acute respiratory infections	Daily 800 and or 3200 IU vitamin D3
17	NCT04459247	Short term, high-dose vitamin D supplementation for COVID-19	Daily 60 000 IU vitamin D3 for a week
18	NCT04335084	A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection	Hydroxychloroquine, vitamin C, vitamin D and zinc
19	NCT04552951	Effect of vitamin D on morbidity and mortality of the COVID-19	Single dose of 100 000 IU vitamin D3
20	NCT04621058	Efficacy of vitamin D treatment in mortality reduction due to COVID-19	Vitamin D supplement in deficient patients
21	NCT04476680	Reducing asymptomatic infection with vitamin D in coronavirus disease	Daily 1000 IU vitamin D3 for 24 weeks
22	NCT04411446	Cholecalciferol to improve the outcomes of COVID-19 patients (CARED)	500 000 IU vitamin D3
23	NCT04596657	Vitamin D3 supplementation to prevent respiratory tract infections	Daily 5000 IU vitamin D3
24	NCT04489628	Tele-health-enabled clinical trial for COVID-19	8 ×50 000 IU vitamin D3
25	NCT04476745	The effect of D3 on selected cytokines involved in cytokine storm in the COVID-19 uninfected Jordanian people	50 000 IU/week for 8 weeks
26	NCT04386850	Oral 25-hydroxyvitamin D3 and COVID-19	Oral 25-Hydroxyvitamin D3
27	NCT03188796	The VITDALIZE study: effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients (VITDALIZE)	Cholecalciferol

(Continues)

TABLE 4 (Continued)

Study	Registry identifier	Title	Interventions
28	NCT04733625	The effect of vitamin D therapy on morbidity and mortality in patients with SARS-CoV 2 infection	Cholecalciferol
29	NCT04868903	Low vs moderate to high-dose vitamin D for prevention of COVID-19	400 IU/day, 4000 IU/day, and 10 000 IU/day doses of vitamin D
30	NCT04825093	Vitamin D supplementation in pregnant women at risk and COVID-19 (VID-WOMAN)	Vitamin D
31	NCT04828538	Vitamin D, Omega-3, and combination vitamins B and C and zinc supplementation for the treatment and prevention of COVID-19	4000 IU Vitamin D vs placebo in one of 3 active arms
32	NCT04952857	Short-term, high-dose vitamin D supplementation in moderate to severe COVID-19 Disease (SHADE-S)	Cholecalciferol
33	NCT04793243	Vitamin D3 levels in COVID-19 outpatients from Western Mexico	10 000 IU/daily for 2 weeks vitamin D3
34	NCT04883203	The effect of vitamin D supplementation on COVID-19 recovery (COVID-VITD)	200 000 IU/mL of cholecalciferol (1 mL) oral solution

TABLE 5 Clinical trials related to anti-hyperglycemic drugs

Study	Registry identifier	Title	Interventions
1	NCT04542213	Dipeptidyl peptidase-4 inhibitor (Dpp4i) for the control of hyperglycemia in patients with COVID-19 (Covid19Dpp4i)	Linagliptin, insulin
2	NCT04371978	Efficacy and safety of dipeptidyl peptidase-4 inhibitors in diabetic patients with established COVID-19	Linagliptin, insulin
3	NCT04604223	Effect of pioglitazone on t2dm patients with COVID-19 (PIOQ8)	Pioglitazone
4	NCT04535700	Clinical trial of pioglitazone treatment in patients with type 2 diabetes mellitus and COVID-19	Pioglitazone
5	NCT04625985	Metformin glycinate, treatment of patients with COVID-19 and severe acute respiratory syndrome secondary to SARS-CoV-2. (DMMETCOV19-2)	Metformin glycinate
6	NCT04473274	GlitazOne treatment for coronavirus hypoxia, a safety and tolerability open label with matching cohort pilot study (GOTCHA)	Pioglitazone
7	NCT04510194	Outpatient treatment of SARS-CoV-2 With ivermectin, fluvoxamine, and metformin (COVID-19)	Metformin, metformin+fluvoxamine, and metformin+ivermectin

reduced the pro-inflammatory cytokines levels and early sacubitril/valsartan administration reduced high sensitivity C-reactive protein levels and increased lymphocyte count in acute heart failure patients and suggested early administration of sacubitril/valsartan in patients with COVID-19.³⁸

3.8 | Antihyperglycemic agents, the RAAS, and COVID-19

Some antihyperglycemic medications have the anti-inflammatory effects (metformin, sulfonyleurea, and dipeptidyl peptidase four inhibitors) in animal models with lung injury, so they can potentially be

protective against COVID-19-induced lung injury.³⁹ Seven clinical trials related to antihyperglycemic agents are depicted in Table 5.

3.9 | Janus-activated kinase inhibitors, the RAAS, and COVID-19

Inhibition of the JAK/signal transducer and activator of the transcription (STAT) signaling pathway has also been suggested as a potential treatment for COVID-19.⁴⁰ Baricitinib is an oral JAK1 and JAK2 inhibitor that has also been suggested for COVID-19 treatment. Baricitinib reduces host cell infection through numb-associated kinases inhibition and has anti-cytokine and anti-inflammatory activity. In a case series

TABLE 6 Clinical trials related to Janus-activated kinase inhibitors

Study	Registry identifier	Title	Intervention
1	NCT04477993	Ruxolitinib for acute respiratory disorder syndrome due to COVID-19 (RUXO-COVID)	Ruxolitinib
2	NCT04359290	Ruxolitinib for treatment of COVID-19 induced lung injury ARDS (RuXoCoil)	Ruxolitinib
3	NCT04399798	Baricitinib for corona virus pneumonia (COVID-19): a therapeutic trial (BREATH)	Baricitinib
4	NCT04402866	TD-0903 for ALI* associated with COVID-19	TD-0903
5	NCT04340232	Safety and efficacy of Baricitinib for COVID-19	Baricitinib
6	NCT04640168	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	Baricitinib+ remdesivir
7	NCT04581954	Inflammatory signal inhibitors for COVID-19 (MATIS) (MATIS)	Ruxolitinib+fostamatinib
8	NCT04401579	Adaptive COVID-19 treatment trial 2 (ACTT-2)	Baricitinib+ remdesivir
9	NCT04320277	Baricitinib in symptomatic patients infected by COVID-19: an open-label, pilot study. (BARI-COVID)	Baricitinib
10	NCT04377620	Assessment of efficacy and safety of ruxolitinib in participants with COVID-19-associated ARDS who require mechanical ventilation (RUXCOVID-DEVENT)	Ruxolitinib
11	NCT04424056	A trial using ANAKINRA, TOCILIZUMAB alone or in association with RUXOLITINIB in severe stage 2b and 3 of COVID19-associated disease (INFLAMMACOV)	Anakinra, Ruxolitinib, and Tocilizumab
12	NCT04321993	Treatment of moderate to severe COVID-19 in hospitalized patients	Baricitinib

TABLE 7 Clinical trials related to resveratrol

Study	Registry identifier	Title	Interventions
1	NCT04799743	The anti-fibrotic therapeutic effects of resveratrol for discharged COVID-19 patients (HKCOVID19Res)	Resveratrol
2	NCT04400890	Randomized proof-of-concept trial to evaluate the safety and explore the effectiveness of resveratrol, a plant polyphenol, for COVID-19	Resveratrol and vitamin D3
3	NCT04542993	Can SARS-CoV-2 viral load and COVID-19 disease severity be reduced by resveratrol-assisted zinc therapy (Reszinate)	Resveratrol and zinc picolinate

of bilateral pneumonia COVID-19 patient's treatment with baricitinib rapidly decreased SARS-CoV-2 viral load and inflammatory markers and was associated with clinical and radiologic improvement.⁴¹ Fedratinib, a specific JAK2 inhibitor, was examined on murine TH17 cells and reduced the expression of IL-17 in these cells. So, fedratinib that enters cells via ACE2-mediated endocytosis has been suggested to suppress the cytokine storm in patients with severe COVID-19.⁴² The clinical trials examining JAK inhibitors are indicated in Table 6.

3.10 | Resveratrol

Resveratrol, a natural polyphenol, is a potent antioxidant that its antiviral activity against a variety of viruses including Middle East

Respiratory Syndrome Coronavirus (MERS-CoV) infection has demonstrated.^{43,44} Three ongoing clinical trials using resveratrol are demonstrated in Table 7.

4 | DISCUSSION

4.1 | ACE2 and SARS-CoV-2 infection

The role of ACE2 in SARS-CoV-2 infection has been confirmed using intravenous MSCs that were both ACE2, and TMPRSS2 negative and free from COVID-19 infection.¹⁴ The ACE2 overexpression in human endothelial cells attenuated the oxidative stress induced by Ang II and subsequent increased monocyte adhesion.¹³ Downregulation of ACE2

in COVID-19 patients has been suggested. Decreased ACE2 levels in these patients may lead to Ang II upregulation and over-activity of the classical RAAS axis. On the other hand, the Ang-(1-7) depletion attenuates the protective effects of the alternative RAAS axis. Upregulation of the pro-inflammatory peptide Ang II contributes to acute lung injury through increased endothelial dysfunction and cytokine storm. The imbalance between both RAAS axes could result in pulmonary, inflammatory/immune, and hematological disturbances.⁴ The ACE2 interaction with the virus decreases its level in infected individuals with SARS-CoV. Therefore, it is suggested that decreased pulmonary ACE2 activity along with cytokines expression is involved in the pathogenesis of lung inflammation.¹² In addition, epigenetic dysregulation (hypomethylation) of ACE2 has been considered a mechanism for increased risk and severity of SARS-CoV-2 infections.¹⁸ Currently, there is no approved effective medication for COVID-19 treatment. However, some researches focused on the therapeutic agents affecting the RAAS pathway, due to its critical role in the regulation of body homeostasis. Moreover, it has been known that ACE2 has a protective role in ARDS, which is a potentially life-threatening form of acute lung injury. Therefore, the development of spike protein-based vaccines and therapeutics with increased ACE2 activity has been suggested as approaches for the management of COVID-19. The beneficial effects of ACE2-enhancing agents in SARS-CoV-2-infected patients might be due to increased ACE2 activity that results in activation of the ACE2-Ang-(1-7)-Mas R component of the RAAS pathway, which is an anti-inflammatory, anti-fibrotic, and anti-oxidative stress signaling.²⁶ The activation of the RAAS pathway through binding of SARS-CoV-2 to ACE2 results in diminished ACE2 levels, which is compatible with systemic manifestations of COVID-19.⁴⁵

The rhACE2 could be used as a potential treatment for hypertension, heart failure, kidney damage, and liver fibrosis.^{21,46,47} The rhACE2 increased the vasculoprotective effects of ACEIs or ARBs.¹³ Simultaneous inhalational administration of rhACE2 and SARS-CoV-2-targeted GapmeR has been suggested as a therapy for COVID-19 as rhACE2 completely eliminates the extracellular virus and GapmeR inhibits viral replication.²² However, rhACE2, with its large molecular size, has limited penetrance and activity against tissue RAAS.⁴⁵ Another suggested compound, sACE2, is produced by ADAM17 in the physiological situations and in SARS-CoV infection that cleaves and releases the extracellular domain of ACE2 (sACE2),^{15,47} with even maintained enzymatic activity.⁴⁸ The sACE2 can compete with ACE2 for binding to the S protein of SARS-CoV and consequently inhibits cellular infection with SARS-CoV.^{25,49} It has been indicated that SARS-CoV-1 spike protein binding to ACE2 activates disintegrin and ADAM17, known as tumor necrosis factor- α (TNF- α) converting enzyme, and induces ACE2 shedding through a process tightly coupled with the production of TNF- α .³⁹ There are controversies about the role of ADAM17 and sACE2 in viral infections. TMPRSS2 enhances the SARS-CoV entry through ACE2 cleavage, which might increase viral uptake, and SARS-S cleavage, which in turn activates the S protein of the virus for membrane fusion.¹⁷ Increasing evidence suggests that the infectious mechanisms of SARS-CoV and SARS-CoV-2 are approximately the same; thus, sACE2 can prevent the SARS-CoV-2 infection.²⁵ Since the sACE2 level is upregulated in the

peripheral blood of IBD patients, it could limit the SARS-CoV-2 infection through competition with full-length ACE2 for binding to SARS-CoV-2.²³ Some studies have figured out the mechanism of binding SARS-CoV-2 spike glycoprotein to ACE2 in order to help design medications that inhibit the spike glycoprotein of SARS-CoV-2, which has a critical role in viral infection and fusion with ACE2.⁵⁰ The CDs, macrocyclic molecules with pyranose units linked by the α -1,4-glycoside chain, can enclose highly hydrophobic molecules in their hydrophobic cavities, so as the complex of CD and sACE2 can effectively improve water solubility of sACE2 and be effective in drug atomization inhalation.²⁵

4.2 | Angiotensin-(1-7)

Angiotensin-(1-7) is one part of the protective the RAAS axis. This peptide binds to AT2R and Mas R. Therefore, in situations with limited AT2R expression, the activation of the Mas R through Ang-(1-7) binding can rebalance the RAAS. Thus, Ang-(1-7) and Mas R agonists could be used in the treatment of patients with severe COVID-19. Stimulation of the ACE2/Ang-(1-7)/Mas R axis has potentially beneficial effects on the respiratory functions, arterial oxygenation, and lung tissue. Angiotensin-(1-7) has a very short half-life (less than 1 minute) in human plasma. However, a modified version of Ang-(1-7) with long-lasting release property, hydroxypropyl- β -cyclodextrin-Ang-(1-7) complex, allows the oral administration of this compound and using this compound in the treatment of COVID-19 patients.²⁴

4.3 | ACE inhibitors and angiotensin receptor blockers

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which suppress the ACE/Ang II/AT1R axis, and mineralocorticoid receptor inhibitors are commonly used in the treatment of hypertensive patients. These agents significantly increase the ACE2 and Ang-(1-7) levels, which is suggestive for their protective effect against virus-induced lung injury.^{12,29} Angiotensin-(1-9) is a competitive inhibitor of ACE; therefore, the administration of an ACEI increases Ang-(1-9) levels through being less catabolized by ACE; moreover, the inhibition of ACE leads to increased availability of Ang I substrate, which in turn is metabolized by ACE2 to Ang-(1-9).⁵¹ The RAAS blockers, especially ARBs, can modulate both systemic and tissue RAAS.⁴⁵ Different RAAS inhibitors have heterogeneous effects on the peptides and enzymes of the RAAS pathway. The ARBs and MCRIs have increased ACE2 expression and activity in clinical and experimental studies, which should be further analyzed prior to being tried in the management of SARS-CoV-2 infection. Further investigation is needed on aliskiren, a direct inhibitor of renin, that reduces ACE2 expression in the context of SARS-CoV-2 infection.⁵² The effect of the RAAS blockade on COVID-19 might be conditional depending on the preexisting RAAS dysregulation associated with concomitant comorbidities and unknown outcomes in these patients.³⁰ The ACE2 may be beneficial in patients with lung injury

and withdrawal of RAAS inhibitors may be harmful in high-risk COVID-19-infected patients with comorbidities.⁵³ Dysregulation of the RAAS axis in cardiovascular diseases, diabetes mellitus, and hypertension could increase the risk or severity of SARS-CoV-2 infection. Due to possible adverse outcomes of RAAS inhibitors in hypertensive individuals infected with COVID-19, an association between severity of the disease and death with advanced aging, and the role of potential confounders such as age should be considered in risk prediction.⁵³ Different effects of RAAS blockers (ACEIs and ARBs) on the levels and activity of the ACE2 in humans, lack of uniform effects of RAAS inhibitors on ACE2 level, and the absence of data related to the effects of RAAS inhibitors on ACE2 expression in the lung using experimental animal models and in humans are issues, which necessitate more clinical trials for elucidation the interaction between SARS-CoV-2 and the RAAS pathway and RAAS inhibitors.⁵³

4.4 | Renin inhibitors

(A) Beta-adrenergic blockers. It has been demonstrated that beta-adrenergic blockers reduced mortality rates in patients with septic shock.⁵⁴ Taking BB before hospitalization in patients with COVID-19 had significantly reduced dyspnea in these patients.³³ Beta-adrenergic blockers negatively regulate renin release from juxtaglomerular cells in the kidneys through their inhibitory effect on the sympathetic system, and also by direct renin inhibition of agents such as aliskiren leading to renin depletion and decreased activity of the RAAS, Ang I, Ang II, and Ang-(1-7).^{37,55} Nebivolol, which is a beta-blocker, increases cardiac ACE2.²⁸ At low doses, BB might be useful in normotensive patients with COVID-19, as they may decrease the entry of SARS-CoV-2 into the cells. Also, it has been demonstrated that BB reduces mortality rates associated with ARDS, septic shock, and respiratory failure.^{37,55} (B) Vitamin D. Vitamin D is another regulator of the RAAS, since the vitamin D-VDR complex suppresses the expression of renin.³⁵ Also, some genes in the RAAS-bradykinin system have VDR binding site. Therefore, it has been suggested that some Food and Drug Administration-approved agents, which reduce BK production and/or signaling, can decrease renin production through vitamin D function and can reduce HA synthesis through targeting HAS 1-3; however, this hypothesis needs to be tested in the well-designed clinical trials for the treatment of COVID-19.³⁵ Vitamin D inhibits renin expression and the ACE/Ang II/AT1R axis, while inducing the expression of ACE2, Mas R, and Ang-(1-7). Thus, this vitamin could have a potential protective role against acute lung injury and ARDS.⁵⁶

4.5 | Kallikrein/kinin pathway and crosstalk with the RAAS

Animal studies and analysis of gene expression^{35,36} indicated an interaction between Ang-(1-7) and ACE with BK and dysregulation of most enzymes involved in the degradation of BK, which results in BK

storm in patients with severe COVID-19. The serine protease kallikrein converts the inactive pre-protein kininogen to BK. Bradykinin induces vasodilation, natriuresis, and hypotension by activating the B2 receptor; moreover, BK is involved in the inflammatory response following injury. Bradykinin is degraded by ACE that is an important aspect of blood pressure regulation.⁵¹ Carboxypeptidases convert bradykinin to (des-Arg9)-bradykinin, an agonist of the B1 receptor, which occurs after tissue injury. In addition, ACE2 degrades (des-Arg9)-BK.⁵¹ There is a crosstalk between the RAAS and the kallikrein/kinin pathways as BK receptor signaling is augmented by Ang-(1-9).³⁵ Interaction between Ang-(1-7) and BK mostly occurs in blood vessels as Ang-(1-7) potentiates BK and also kinins mediate the vascular functions of Ang-(1-7). Furthermore, all components of the kallikrein-kinin system are expressed in kidney, which exerts a paracrine influence on local nephron functions. This system produces local concentrations of BK in the kidneys much more than those that exist in the blood and modify the actions of Ang-(1-7).⁵

4.6 | Hyaluronic acid, the RAAS and BK

It has been suggested that alteration in the HA synthesis and degradation might cause an increase in the HA concentrations in the bronchoalveolar space of the lungs that can form a viscous hydrogel with a negative impact on gas exchange, along with the induced vascular hyperpermeability by BK. Hyaluronic acid, a polysaccharide found in most connective tissues, can trap and bind to water and produce a hydrogel with a stiff viscous quality. In addition, both BK and the RAAS pathways have been known to tie to HA.³⁵ COVID-19 might downregulate Ang II production, which is consistent with the CD44 expression decrease seen in the BAL fluid of SARS-CoV-2-infected patients. Since Ang II is the catalytic product of ACE that downregulates ACE2 expression, it seems that the reduced ACE expression results in upregulation of the ACE2 in BAL specimens of COVID-19 patients with increased Ang-(1-9), a BK-augmenting peptide, and the exacerbation of the BK-effects, such as pain sensitization and enhanced vascular permeability.³⁵

4.7 | Nephilysin, the RAAS, and COVID-19

There is disagreement related to the role of NEP in COVID-19. Nephilysin, a neutral endopeptidase, is a zinc metalloendopeptidase that is highly expressed in the kidneys and lungs. Decreased Ang II formation and directing Ang I to generate Ang-(1-7) and degradation of BKs by NEP and prevention of the inflammatory cells' recruitment has suggested NEP as a potential therapeutic agent in COVID-19. The NEP expression is upregulated by some medications (dexamethasone and valproic acid), hormones (androgens and estrogen), and natural substances and accordingly, the recombinant NEP can be considered for possible therapeutic goals.³⁷ However, increased NEP expression and activity by cytokines and in ARDS patients and also positive impact of sacubitril/valsartan on acute heart failure might suggest targeting NEP in the treatment of COVID-19 patients.⁵⁷

4.8 | Antihyperglycemic agents, the RAAS and COVID-19

The RAAS plays an essential role in glucose homeostasis. It seems that ACE2 acts with a compensatory mechanism for hyperglycemia-induced RAAS activation and has protective role in diabetes. Since some antihyperglycemic medications such as insulin, peroxisome proliferator-activated receptor- γ agonist (pioglitazone), and glucagon-like peptide 1 (liraglutide) have both modulatory effects on the RAAS and anti-inflammatory effects and due to the anti-inflammatory effects of some of these agents in animal models with lung injury, it might be inferred that they can potentially be protective against COVID-19-induced lung injury.³⁹

4.9 | Janus-activated kinase inhibitors the RAAS and COVID-19

Angiotensin II activates the JAK2/STAT pathway that is critical for Ang II-induced hypertension development. Chronic blockade of JAK2 by its inhibitors has prevented Ang II-induced hypertension in animals.⁵⁸ Baricitinib is one of the proposed agents for COVID-19 treatment as an antiviral agent with anti-cytokine activity. The mechanism of reducing viral infection of host respiratory cells by baricitinib is through its high affinity inhibitory effect on numb-associated kinases such as AAK1, BIKE, and GAK kinases. Its anti-cytokine activity is through the inhibition of cytokine signaling.⁴¹ Also, fedratinib, as a specific JAK2 inhibitor, has been suggested for the cytokine storm suppression in patients with severe COVID-19.⁴²

4.10 | Resveratrol

Antioxidant, anti-inflammatory, and antiviral effects of resveratrol suggested this compound to be studied in the treatment of patients with COVID-19. Resveratrol suppresses Ang II that might decrease inflammation. Also, antioxidant effects of resveratrol in the lung might reduce lung damage. This compound is safe to use with maximum of 2 to 3 g daily.^{43,44,59} However, its advantage in COVID-19 patients as an adjunct to other therapies should be studied.

5 | CONCLUSION

The SARS-CoV-2 enters and infects the human cells through binding to the ACE2 component of the RAAS. There is a crosstalk between the RAAS and kallikrein/kinin pathway and the association of both pathways with HA degradation and NEP activity. Regarding the role of RAAS especially the ACE2 component of the system in the pathogenesis of COVID-19, treatments have been suggested using rhACE2 and applying GapmeR technology with rhACE2 and metalloproteinase for producing sACE2 from full-length ACE2, and Ang-(1-7) infusion, and also medications with the inhibitory effects on SARS-CoV-

2 S-glycoprotein have been proposed. Accordingly, ACEIs, ARBs, and MCRIs, which are prevalent medications in hypertensive patients, are agents that significantly enhance the ACE2 and Ang-(1-7) levels, which can be suggestive for their role as therapeutics against SARS-CoV-2 infection. However, due to different effects of RAAS blockers on levels and activity of the ACE2 in humans, lack of uniform effects of RAAS inhibitors on ACE2 level, and the absence of data related to the effects of RAAS inhibitors on ACE2 expression in the lung using experimental animal models and in humans, we should wait for the results of clinical trials related to the benefit and safety of RAAS inhibitors. Beta-adrenergic blockers, which negatively regulate renin release from juxtaglomerular cells, and vitamin D, as a regulator of the RAAS and renin expression, are proposed therapeutics in the treatment of COVID-19. In addition, due to modulatory effect on the RAAS and also anti-inflammatory effects, some antihyperglycemic agents could be potentially protective against COVID-19-induced lung injury. Furthermore, activation of the JAK2/STAT pathway by Ang II, which is the mainstay of Ang II-induced hypertension development, suggests the inhibition of the JAK/STAT signaling pathway as a potential treatment for COVID-19. Finally, resveratrol, an antioxidant that can suppress Ang II, has been suggested as an adjunct to other therapies. Regarding the aforementioned proposed potential therapies for COVID-19, there are many clinical trials whose results might change the treatment strategies of SARS-CoV-2 infection. Therefore, we should still wait and watch for published results of well-organized clinical trials on the efficacy and safety of the mentioned agents in the treatment of COVID-19.

CONFLICT OF INTEREST

None.

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