Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [4] November 2022 : 324-329

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Utilizing ACE 2 receptor for covid-19 treatment: turning foes into friends

Suman Rohilla*[1], Tripti Arora[1], Vaibhav Walia[1]
SGT College of Pharmacy,
Shree Guru Gobind Singh Tricentenary University, Gurugram
***Corresponding author Email:** rh.suman@gmail.com

ABSTRACT

An unusual, highly contagious coronavirus disease COVID-19 caused by recently identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a clinic threat and presented a major health crisis worldwide in the absence of specific vaccine or antiviral drugs. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2), a type 1 transmembrane receptor to infect host cell and primarily target type II alveolar cells profusely rich in ACE2 expression. Although SARS-CoV-2 infect people of all age group but older population and persons with co-morbid conditions are at greater risk. Hypertension, renal impairment and diabetes are the most common underlying co-morbidities reported in covid-19 patients that contribute to disease worsening and more severe clinical complications leading to death. SARS-CoV-2 invasion induced ACE2 receptor down-regulation with a subsequent imbalance between angiotensin II and angiotensin 1-7 levels plays a vital role in the pathogenic advancement of the disease. Excess accumulation of angiotensin II causes distressed immune functions and hyperactive inflammatory system leading to multi-organ injuries thus contributing in covid-19 disease progression. In the current review the dual role of the ACE2 receptor operating as an entry door to SARS-Cov-2 as well as a key player in the pathogenic progression of the disease is discussed. We further put forward a hypothesis to exploit ACE2 receptor functions to suppress disease progression and reduce mortality in covid-19 patients.

Keywords: *SARS-Cov-2, ACE2 receptor, xanthenone, covid-19*

Received 02.10.2022 Revised 15.10.2022 Accepted 21.11.2022

INTRODUCTION

The unprecedented global spread of COVID-19, a highly contagious, life threatening disease cause by a newly identified severe acute respiratory syndrome CoV-2 (SARS-CoV-2)has become a clinical threat to the world [1].Several retrospective analyses have evaluated the risk factors associated with disease severity and postulated a direct association between any pre-existing pathological conditions (underlying disorders such as hypertension, diabetes, renal impairment etc) and severity of covid-19 disease with cardiovascular ailments being the most prevalent comorbidity reported in covid-19 patients [2-6]. Presence of more than one comorbidity further intensifies risk of severe outcomes including lung injury and acute respiratory distress syndrome (ARDS) leading to death. Phylogenetic and genomic analysis of SARS-CoV-2 relate its origin with the bat SARS-like-CoVZXC21(nucleotide identity 89%) and human SARS-CoV (82%) [7]. SARS-CoV-2 is now known to utilize angiotensin-converting enzyme 2 (ACE2), a type 1 transmembrane receptor to infect the host cell through fusion between the viral and cellular membrane assisted by transmembrane TMPRSS2 serine protease [8,9]. Receptor binding domain is present in S1 subunit of the spike glycoprotein whereas S2 subunit contains the fusion peptide. TMPRSS2 a host serine protease is critical for post cleavage priming at the S1/S2 region and activating the viral and cellular membrane fusion. It is believed that increased infectivity of SARS-CoV-2 is due to greater binding affinity ofSARS-CoV-2 spike towards ACE2 receptor as compared to SARS [10,11]. ACE2 receptor is a vital element of renin angiotensin system (RAS), a ubiquitous hormonal system vital to maintain hydroelectrolytic balance and vascular pressure. ACE2 receptor plays a counter regulatory role and catalyzes the hydrolysis of key vasoconstrictor peptide angiotensin II to angiotensin 1-7 and formation of angiotensin 1-9 from angiotensin I [12,13]. Angiotensin II is a multifunctional nonhemodynamic molecule which exert its vasoconstritory, pro-inflammatory, profibrotic and oxidative effects *via* G-protein coupled AT-1 type receptor [14]. Angiotensin 1-7 and angiotensin 1-9 counteract the angiotensin II mediated effects and produce vasodilatory, anti-proliferative, anti-inflammatory, anti-fibrotic and anti-thrombotic effects *via* G-protein coupled Mas receptor [15]. ACE2 thereby conducting the degradation of angiotensin

I and angiotensin II physiologically balances renin angiotensin system mediated effects. Several reports have acknowledged the protective effects of ACE2 in lung injury in animal models of ARDS [16,17]. Various studies also supported cardio-protective [18,19]as well as renoprotective [20,21] effects of ACE2. Also ACE2 is now recognized as entry portal for coronaviruses SARS and SARS-2-Covs [8,22].

ACE2 receptor in Covid-19 pathology

ACE2 receptor not only serves as the entry point for the virus but has implications in pathological progression of the disease [23]. The physiological distribution and expression of ACE2 largely affects the susceptibility and spread of infection in target organs and presentation of clinical manifestations in covid-19 patients. Type II alveolar epithelial cell are profusely rich in ACE2 receptor expression and represent the most vulnerable target to SARS-CoV-2 [24]. ACE2 receptor is expressed in heart, vascular endothelial cells, kidney, liver, intestinal enterocytes as well as in soluble form in plasma and urine [25,26]. Upper respiratory tract is the major target of SARS-CoV-2 causing initial flu like symptoms but disease progression further involves multiple organs affecting heart and kidney more severely. It is speculated that patients suffering from hypertension or diabetes who are on treatment therapy with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) might have increased ACE2 receptor expression and might predispose patients to COVID-19 infection. [27,28]. However, scientific data in support of this assumption is quite inconsistent. Overexpression of ACE2 receptor is theoretically related with increased susceptibility to infection. Further investigation is impending in this direction to understand the exact relationship between the two. Shreds of evidence are now mounting in the support of the notion that use of RAS inhibitors is not associated with increased COVID-19 infection or disease severity [29-31]. Moreover, it is proposed that use of RAS inhibitors greatly reduced the risk of severe clinical outcomes and confers protective effects in COVID-19 patients as compared to other antihypertensive drugs [32,33].

The SARS-CoV-2 infection causes ACE-2 receptor downregulation after exploitingit for internalization [23]. Virus-induced downregulation of ACE-2 receptorresults in loss ofcatalytic activities of ACE-2. Besides diminished organ protective effects, ACE2 is also not available to perform its salutary physiological functionsof hydrolyzing the vasoconstrictor peptide angiotensin II.Consequent accumulation of angiotensin II and uncontrolled AT-1 type receptor activationresults in abnormal vasoconstriction, endothelial dysfunction, pulmonary fibrosis, hypertension, hypercoagulation, thrombosis and amplified inflammationthus contributing in overall enhanced disease severity.Increased pulmonary vascular permeability due to angiotensin II accumulation further contribute to intensified lung injury [16,23]. Overactivation of angiotensin II mediated evil effects causes far reaching deleterious effects in immune-compromised/co-morbid covid-19 patients. Angiotensin II is known to dysregulates adaptive immune coordination and upsurge inflammatory chemokines and cytokines production[34]. Augmented release of pro-inflammatory mediatorsleading to cytokine storm acrucial factor involved in disease advancement further intensifies the lung inflammatory damage in covid-19 patients with consequent ARDS and even death. Moreover, elevatedplasma level of angiotensin II is reported as an indicator of viral load in covid-19 patients and is directly related to disease severity [35].Angiotensin-1-7 deficiency owing to interrupted degradation of angiotensin II due to ACE2 downregulation along with a predestined breakdown of angiotensin-1-7 into inactive peptides aid further in the complexity of disease severity. These observationspoint to a critical role of the disturbed RAS system in the signalingof abnormal cellular and molecular events accountable forthe disease progression of covid-1. An increased level of a soluble form of ACE2 enzyme is considered a biomarker for myocardial infarction [36]. Angiotensin II further promotes the ADAM-17 mediated cleavage of membrane-bound ACE2 [37]. In ACE2 deficit hearts,angiotensin II accumulation and reduced angiotensin-1-7 levels is linkedto enhanced production of reactive oxygen species in the infarct-related zone along with augmented inflammatory response [38]. Amplified release of plasma pro-inflammatory cytokines (IL-1b, IL-1, IL-7, IL-8, IL-9, IL-10, IFNγ, monocyte chemoattractant protein (MCP1) is associated with disease progression instigating cytokine storm syndrome and consequent ARDS and even death in more severe cases of covid-19. SARS-CoV-2 invasion induced down-regulation of ACE2 receptor resulting in disturbed RAS system with a subsequent unsolicited accumulation of angiotensin II is a key etiological factor in SARS-CoV-2 infection pathogenesis advancement. The above findings clearly indicate that disturbed RAS system and hyperactive inflammation system are key players in SARS-Cov-2 infection and employing the methods to restore the RAS balance represents a viable approach to resist COVID-19 disease progression.

ACE2 in covid-19 treatment

The exaggerated pattern of disease progression associated with theSARS-CoV-2 induced downregulation of ACE2 producing more severe outcomes in covid-19 patients gives rise to the hypothesis that enhanced expression and upregulation of ACE2 through the use of ACE2 enhancers (Xanthenone, DIZE), upsurged levels of ACE2 by exogenous administration of recombinant human soluble ACE2 (rhACE2)along with

AT1 AR blockers(losartan)will result in substantial reversal of devastating tissue injury.Additionally, synthetic mas receptor agonists stimulating G-protein coupled Mas receptor would control detrimental inflammatory and fibrosis effects and counteract angiotensin II mediated tissue injury as depicted in figure 1.

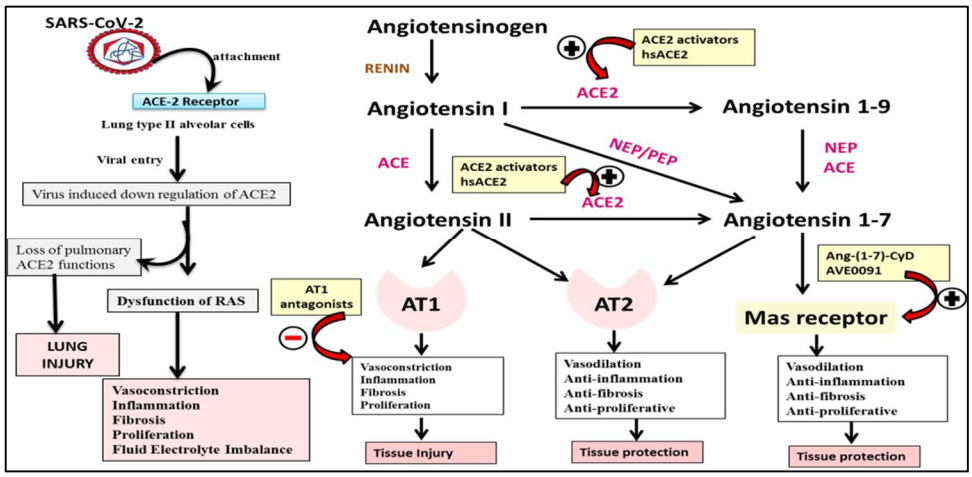

Figure 1: **Implications of ACE2 downregulation mediated pathogenesis in Covid-19 disease**.

The proposed pathway by which ACE2 activators, AT1 Receptor Blockers could enhance ACE2 mediated degradation of angiotensin II to produce vasodilator peptide angiotensin 1-7. Mas receptor agonists mimics the tissue protective effects exerted by vasodilatory angiotensin 1-7 peptide.

ACE 2 Activators: Restoration of ACE2 through use of ACE2 activators will recuperate local tissue protective, anti-inflammatory, anti-prolifrative effects of ACE2. Revival of ACE2 will also aid in systemic balance of renin–angiotensin–system functioning and resist undesired over accumulation and hyperactivity of vasoconstrictor peptide angiotensin II. ACE2 enable essential catabolism of angiotensin II for generating vasodilatory peptide angiotensin-1-7 which exert anti-inflammatory, anti- proliferative, anti-inflammatory, anti-fibrosis and anti-oxidant effectsleading tissue protection. ACE2 activator 1-[(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one(xanthenone)is reported to exhibit noteworthy hypotensive and cardiac protective activities in variousexperimental studies [39, 40.Xanthenone is also reported to reduce vascular remodeling and fibrosis in an animal model of pulmonary hypertension (PH) in a rats [41].Additionally potent antithrombotic effects of xanthenone further justify its promising use in ameliorating the coagulation abnormalities in covid-19 patients [42].

Recombinant human soluble ACE2 (rhACE2): An alternative approach to increase ACE2 activity is exogenous supply of recombinant human ACE2 (rhACE2). It has been reported to display potential anti-inflammatory effects and attenuate severe acute lung injury in various animal experimental studies [43,44] Interestingly, rhACE2 infusion is allied to lessen the interleukin-6 (IL-6) concentrations in patients with ARDS in a pilot study [45].Raised levels of IL-1β a pro-inflammatory cytokine and its natural antagonist detected in the blood and alveolar lavage sample of covid-19 patients is correlated with hyper-inflammatory response and linked complications [46]. rhACE2 attenuates the deleterious effects exerted by angiotensin II by promoting its degradation and endeavors to restore the altered balance between angiotensin II and angiotensin 1-7 levels by increasing the cellular activities of ACE2. Additionally, rhACE2 might neutralize the spike glycoprotein and through competitive inhibition prevent SARS-CoV-2 interaction with the host cell receptors [47]. The data from *in vitro* studies documents rhACE2 mediated SARS-CoV-2 inhibitory effects [47]. APN01, a recombinant form of ACE2 developed by APEIRON biologics currently under evaluation to assess its potential benefit in treating SARS-CoV-2 induced pneumonia. The above findings advocate a dual role of rhACE2 in preventing the spike glycoprotein interactions with the receptor as well as anti-inflammatory potential by reducing the concentration of a pro-inflammatory cytokine IL-6 a prime culprit involved in disease advancement in covid-19. Recombinant human soluble ACE2 represent a promising drug candidate against SARS-CoV-2 both early as well as late stages of infection.

Angiotensin AT1 receptor blockers (ARB): AT1 receptor antagonists would certainly mitigateevil effects of angiotensin II in absence of cellular ACE2 activity. Moreover unavailability of AT1 receptor for binding would direct angiotensin II towards AT2 type receptor.Angiotensin II exerts tissue protective effects through AT2 type receptor activation.

Mas receptor agonists: Angiotensin-1-7 a natural agonists of mas receptor is reported to display cardioprotective properties [48],lessen angiotensin II-induced cardiac remodeling by attenuating

interstitial and perivascular fibrosis [49], anti-fibrotic effects and protect from lung injury [50].Increasing endogeneous concentration of angiotensin-1-7 either by improved ACE2 directed angiotensin II degradation or exogeneous administration of angiotensin-1-7 will help reversing tissue injury. However poor pharmacokinetic profile limits its use for clinical purposes. Alternatively, Ang-(1-7)-CyD, a cyclized form of angiotensin-1-7 with hydroxypropyl β-cyclodextrin is formulated and reported to produce cardiac protective [51] and antithrombotic effects upon chronic administration [52]. Another imidazole based synthetic agonist of mas receptor AVE0091 with proven beneficiary effects in cardiac and renal disorders [53,54] certainly holds potential in controlling altered RAS mediated ill effects and reducing disease severity in covid-19. Taking together above facts it is suggested that activation of mas receptor will harvest beneficiary effects in controlling disease progressing and reduced mortality in covid-19 patients.

CONCLUSION

SARS-CoV-2 is a highly infectious virus which utilizes ACE2 receptor to gain entry in the host cell. ACE2 is a metalloprotease membrane bound receptor that is abundantly expressed in various tissues including lungs, heart, endothelium and kidneyand act as a double edged sword in covid-19 disease pathology. On one side it serves as entry gateway for SARS-CoV-2 while on other hand it offers opportunities for development of ACE2 based therapeutic strategies to combat covid-19 disease advancement. Hypertension, renal impairment and diabetes are the most common underlying co-morbidities that contribute to the covid-19 pathological progression and more severe clinical complications leading to death. ACE inhibitors and angiotensin receptor blockers constitute the most commonly recommended treatment for above indications. It is theoretically alleged that increased expression of ACE 2 associated with RAS based treatment therapy (ACE inhibitors/AR blockers) is directly related with the susceptibility to SARS-CoV-2 infection. However scientific evidences are now available which clearly contradict this assumption and state that RAS based treatment therapy does not increase the risk of Covid-19 or more severe complications rather display protective effects against disease advancement.SARS-CoV-2 internalization induced ACE2 down regulation exaggerate the disease pathological progression due to loss of cellular ACE2 activity and consequent altered RAS system. Resultant imbalance between angiotensin II and angiotensin 1-7 peptides leads to the inflammatory, proliferative, fibrotic and tissue detrimental effects and contribute to the lung injury instigated by SARS Cov-2 infection. Accompanied damaging effects are more serious in covid patients with underlying pathological conditions such as cardiac or renal disorders. Increasing ACE2 membrane expression using xanthenone or by increasing the tissue activity of ACE2 either by exogeneous soluble ACE2 or AR blockers dependent unregulated expression would restore the RAS systemic functioning and avert inflammation associated tissue damage in covid-19. The idea of using ACE2 activators in combination with AT1 AR blockers in covid-19 patient has potential in controlling the disease worsening and prevent development of life threatening indications such as acute lung injury, hypertension persuaded pathophysiology, renal damage and ARDS etc.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest. The research received no specific grant from any funding agency in the public, community, or non-for profit sectors.

REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. The Lancet 2020; 470-473.https://doi.org/10.1016/S0140-6736(20)30185-9.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020; 395(10223), 497-506,https://doi.org/doi:10.1016/S0140-6736(20)30183-5.
3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. Jama 2020; 323 (11), 1061–1069. https://doi.org/doi:10.1001/jama.2020.1585.
4. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020; 94, 91-95, https://doi.org/doi:10.1016/j.ijid.2020.03.017.
5. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J 2020 (in press), https://doi.org/10.1183/13993003.00547-2020.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395, 1054–62.https://doi.org/10.1016/S0140-6736(20)30566-3.

7. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020; 9(1), 221-236, https://doi.org/doi:10.1080/22221751.2020.1719902.
8. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579, 270–273 https://doi.org/10.1038/s41586-020-2012-7.
9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271-280.https://doi.org/10.1016/j.cell.2020.02.052.
10. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science, 2020; *367*(6483), 1260-1263,https://doi.org/doi:10.1126/science.abb2507.
11. Chen, Y., Guo, Y., Pan, Y., & Zhao, Z. J. (2020). Structure analysis of the receptor binding of 2019-nCoV. Biochemical and Biophysical Research Communications. https://doi.org/ 10.1016/j.bbrc.2020.02.071
12. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother. 2017; 94, 317-25.https://doi.org /10.1016/j.biopha.2017.07.091
13. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends in pharmacological sciences. 2004; 25(6), 291-4.https://doi.org/10.1016/j.tips.2004.04.001
14. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010; 2(7), 247-57.https://doi.org/10.1002/emmm.201000080.
15. Santos, R. A., Simoes e Silva, A. C., Maric, C., Silva, D. M., Machado, R. P., de Buhr, I., … Walther, T. (2003). Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. Proceedings of the National Academy of Sciences of the United States of America, 100(14), 8258–8263.].
16. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005; 436(7047):112-6.
17. Imai Y, Kuba K, Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Exp Physiol 2008; 93:543–548.https://doi.org/10.1113/expphysiol.2007.040048.
18. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveirados- Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002; 417:822-828.
19. Kassiri Z, Zhong J, Guo D, Basu R, Wang X, Liu PP, Scholey JW, Penninger JM, Oudit GY. Loss of angiotensin-converting enzyme 2 accelerates maladaptive left ventricular remodeling in response to myocardial infarction. Circ Heart Fail 2009; 2: 446-455.
20. Dilauro M, Zimpelmann J, Robertson SJ, Genest D, Burns KD. Effect of ACE2 and angiotensin-(1-7) in a mouse model of early chronic kidney disease. Am J Physiol Renal Physiol 2010; 298:F1523-F1532.
21. Silveira KD, Pompermayer Bosco KS, Diniz LR, Carmona AK, Cassali GD, Bruna-Romero O, de Sousa LP, Teixeira MM, Santos RA, Simões e Silva AC, Ribeiro-Vieira MA. ACE2-angiotensin-(1-7)-Mas axis in renal ischaemia/ reperfusion injury in rats. Clin Sci (Lond) 2010; 119:385-394.
22. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends in pharmacological sciences. 2004; 25(6), 291-4.https://doi.org/10.1016/j.tips.2004.04.001
23. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11(8):875e9. https://doi.org/10.1038/nm1267.
24. Jia HP, Look DC, Shi L et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. Journal of virology. 2005; 79(23), 14614-21.https://doi.org/10.1128/JVI.79.23.14614-14621.2005.
25. Tipnis SR, Hooper NM, Hyde R, *et al.* A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 2000; 275: 33 238–33 243.
26. Donoghue M, Hsieh F, Baronas E, *et al.* A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. Circ Res 2000; 87: E1–E9.
27. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005; 111(20):2605-2610.https://doi.org/10.1161/CIRCULATIONAHA.104.510461
28. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8: e21.
29. [de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensinaldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020; published online May 14. https://doi.org/10.1016/S0140-6736(20)31030-8.]
30. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 2020; published online April 23. DOI:10.1001/ jamacardio.2020.1624.
31. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensinaldosterone system blockers and the risk of Covid-19. N Engl J Med 2020; published online May 1. DOI:10.1056/NEJMoa2006923.
32. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020; published online April 17. DOI:10.1161/ CIRCRESAHA.120.317134.

33. Bean DM, Kraljevic Z, Searle T, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multisite UK acute hospital trust. medRxiv 2020; published online April 11.DOI:10.1101/2020.04.07.20056788 (preprint).
34. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020; 3, 1-6.https://doi.org/10.1007/s12250-020-00207-4.
35. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364–74. doi: 10.1007/s11427-020-1643-8.
36. Epelman S, Shrestha K, Troughton RW, Francis GS, Sen S, Klein AL, Tang WW. Soluble angiotensin-converting enzyme 2 in human heart failure: relation with myocardial function and clinical outcomes. Journal of cardiac failure. 2009 Sep 1;15(7):565-71.
37. Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Putko B, Kassiri Z, Turner AJ, Oudit GY. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. J Mol Cell Cardiol 2014; 66: 167-176.
38. Kassiri Z, Zhong J, Guo D, Basu R, Wang X, Liu PP, Scholey JW, Penninger JM, Oudit GY. Loss of angiotensin-converting enzyme 2 accelerates maladaptive left ventricular remodeling in response to myocardial infarction. Circulation: Heart Failure. 2009 Sep 1;2(5):446-55.
39. Structure-based identification of small-molecule angiotensin-converting enzyme 2 activators as novel antihypertensive agents. Hernández Prada JA, Ferreira AJ, Katovich MJ, Shenoy V, Qi Y, Santos RA, Castellano RK, Lampkins AJ, Gubala V, Ostrov DA, Raizada MK Hypertension. 2008 May; 51(5):1312-7.].
40. Angiotensin-converting enzyme 2 activation protects against hypertension-induced cardiac fibrosis involving extracellular signal-regulated kinases. Ferreira AJ, Shenoy V, Qi Y, Fraga-Silva RA, Santos RA, Katovich MJ, Raizada MK Exp Physiol. 2011 Mar; 96(3):287-94]
41. Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, Castellano RK, Ostrov DA, Oh SP, Katovich MJ, Raizada MK Am J Respir Crit Care Med. 2009 Jun 1; 179(11):1048-54.
42. ACE2 activation promotes antithrombotic activity.Fraga-Silva RA, Sorg BS, Wankhede M, Dedeugd C, Jun JY, Baker MB, Li Y, Castellano RK, Katovich MJ, Raizada MK, Ferreira AJMol Med. 2010 May-Jun; 16(5-6):210-5.
43. [Gu H., Xie Z., Li T., Zhang S., Lai C., Zhu P. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep. 2016;6:19840. doi: 10.1038/srep19840.]
44. Zou Z., Yan Y., Shu Y., Gao R., Sun Y., Li X. Angiotensin-converting enzyme 2 protects from lethal avian influenza a h5n1 infections. Nat Commun. 2014;5:3594. doi: 10.1038/ncomms4594.]
45. [Khan A., Benthin C., Zeno B., Albertson T.E., Boyd J., Christie J.D. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21(1):234. doi: 10.1186/s13054-017-1823-x.]
46. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cheng, Z. (2020a). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*, *395*(10223), 497-506.
47. Lei, C., Fu, W., Qian, K., Li, T., Zhang, S., Ding, M., & Hu, S. (2020). Potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig. *BioRxiv*.
48. Al-Maghrebi, Benter IF, Diz DI. Endogenous angiotensin-(1-7) reduces cardiac ischemia-induced dysfunction in diabetic hypertensive rats. Pharmacol Res 2009;
59: 263-268.
49. McCollum LT, Gallagher PE, Ann Tallant E. Angiotensin-(1-7) attenuates angiotensin II-induced cardiac remodeling associated with upregulation of dualspecificity phosphatase 1. Am J Physiol Heart Circ Physiol 2012; 302: H801-810.
50. Meng Y., Yu C.H., Li W. Angiotensin-converting enzyme 2/angiotensin-(1–7)/Mas axis protects against lung fibrosis by inhibiting the MAPK/NF-kappaB pathway. Am J Respir Cell Mol Biol. 2014;50:723–736.
51. Marques FD, Ferreira AJ, Sinisterra RD, Jacoby BA, Sousa FB, Caliari MV, Silva GA, Melo MB, Nadu AP, Souza LE, Irigoyen MC, Almeida AP, Santos RA. An oral formulation of angiotensin-(1-7) produces cardioprotective effects in infarcted and isoproterenol-treated rats. paHypertension 2011; 57: 477-83.]
52. Fraga-Silva RA, Costa-Fraga FP, De Sousa FB, Alenina N, Bader M, Sinisterra RD, Santos RA. An orally active formulation of angiotensin-(1-7) produces an antithrombotic effect. Clinics (Sao Paulo) 2011; 66: 837-841.]
53. .[Barroso LC, Silveira KD, Lima CX, Borges V, Bader M, Rachid M, Santos RA, Souza DG, Simões e Silva AC, Teixeira MM. Renoprotective Effects of AVE0991, a Nonpeptide Mas Receptor Agonist, in Experimental Acute Renal Injury. Int J Hypertens 2012; 2012: 808726.]
54. Ferreira AJ, Oliveira TL, Castro MC, Almeida AP, Castro CH, Caliari MV, Gava E, Kitten GT, Santos RA. Isoproterenol-induced impairment of heart function and remodeling are attenuated by the nonpeptide angiotensin-(1-7) analogue AVE 0991. Life Sci. 2007; 81: 916-923.

CITATION OF THIS ARTICLE

S. Rohilla, T. Arora, V. Walia Utilizing ACE 2 receptor for covid-19 treatment: turning foes into friends ,Bull. Env.Pharmacol. Life Sci., Spl Issue [4] 2022 : 324-329