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Coronavirus And Diabetes-Future Directions: A Review

Abhinav Choubey[1, a], Jyoti Sharma[1, b], Prosenjit Mondal[a, *] and Dhale D. A. [c, *]

[a]School of Basic Sciences, Indian Institute of Technology Mandi-175005, HP (India)

[b]Departmentof Zoology, Sant Gaahira Guru Rameshwar College, Lailunga, Raigarh- 496113 Chhattisgarh (India)

[c]Post-Graduate Department of Botany, SSVP Santha's L.K. Dr. P. R. Ghogrey Science College, Dhule-424005, MS (India)

***Corresponding Authors Email**: drdattadhale@gmail.com ; prosenjit@iitmandi.ac.in

1-Contributed equally

ABSTRACT

Novel Coronavirus-2019 (nCoV-2019) was recognized in the Hubei province of Wuhan in China in December 2019. Epidemiological studies confirmed that age and people with pre-existing conditions, including diabetes (from mild to severe), CVD, hypertension, obesity, and chronic lung disease are at a very high risk of severe illness from coronavirus (COVID-19) are also associated with increased mortality. The reason behind this challenge is a low understanding of the molecular co-existence of the nCoV-2019 patient with diabetes and related comorbidities. At present, what we know about virus entry is the following, the viral spike (S) coat protein engages the human angiotensin-converting enzyme2 (ACE2) cell surface protein to invade the host cell. On the other hand, ACE2 expression/activity is reported to decrease with diabetic conditions (and related complications), and interestingly ACE2 expression gets upregulated during anti-diabetic therapies such as thiazolidinediones. The ACE2 upregulation provides rescuing effects in this metabolic illness; however, contrarily, ACE2 upregulation provides a suitable environment for this opportunistic virus to find more ACE2 and invade new cells. Interestingly ACE2 polymorphism and tissue-specific expression/activity of ACE2 are associated with various metabolic diseases and may act as an independent factor for a predisposing individual toward COVID-19 infection. We here depicted commonly shared signaling pathways between nCoV-2019 and mild to severe diabetes. Thus, overall the combination of ACE2 polymorphism, differential expression of ACE2, and the ability of some therapeutic agents to enhance ACE2 makes such individuals more prone to COVID-19 infection. We concluded this review with some exploratory novel approaches that can be utilized for targeting nCoV-2019 patients with certain mild to severe metabolic comorbidities.

Keywords: Novel Coronavirus-2019 (nCoV-2019), angiotensin-converting enzyme2 (ACE2), diabetes, insulin, COVID-19, and cytokine storm.

1. Introduction

An extraordinary outbreak of pneumonia-like condition presenting clinical symptoms of fever, dyspnea, dry cough, and lung damage in Wuhan city of China began in December 2019[1]. A novel COVID-19 was identified as a causal agent behind this and the World Health

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Organization declared this outbreak as a pandemic disease[2]. The rapid progression of the disease, which already intruded almost 213 countries and making around 25 million people at risk, has directed everyone to look into this. Despite various efforts like social distancing and lockdown, the progression of this disease is still increasing at an alarming speed. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and manifests as a pathophysiological condition majorly in the lower respiratory tract. It is a highly contagious agent as it enters the cells and is capable of the host to host transmission.

Risk factors: People with pre-existing pathological conditions like heart disease, asthma, COPD, metabolic diseases including diabetes, hypertension and personal states such as smoking, e-cigarettes (vaping), blood "ABO" group individual and elder are more prone to COVID-19 infection[3]. Moreover, ACE2 polymorphism is also an important risk factor that makes the individual sensitive to COVID-19 infection[4]. The molecular mechanism responsible for the increased disease severity in patients with these comorbidities is one of the major challenges that need to be addressed.

2. COVID-19 Life cycle: Targets

COVID-19 follows a complex receptor recognition pattern and enters the host cells. The COVID-19 life cycle starts from the recognition of these spike proteins with host receptors followed by fusion and replication to endosomal mediated delivery. At present, what we know about virus entry is the following, the viral spike (S) coat protein engages the human angiotensin-converting enzyme2 (ACE2) cell surface protein to invade the host [5–7]. ACE2 belongs to the M2 zinc metalloproteinase family and thus has been claimed as an excellent receptor for this virus[8, 9]. COVID-19 infects the host cell through its spike (S) glycoprotein after it gets cleaved into two subunits S1 and S2[10]. S1 has an affinity for ACE2 as it contains a receptor-binding domain, which allows the virus to bind directly to the peptidase domain of ACE2. After the virus binds to ACE2, the S2 subunit of this virus helps it to fuse down to membrane[5]. After the virus enters the cell, it makes countless copies to attack new cells in the host system and mainly spreads during close contact between people (Fig-1). Considering the above facts, dynamic interaction between ACE2- viral spikes (S) coat protein is a major area of interest to target COVID-19.

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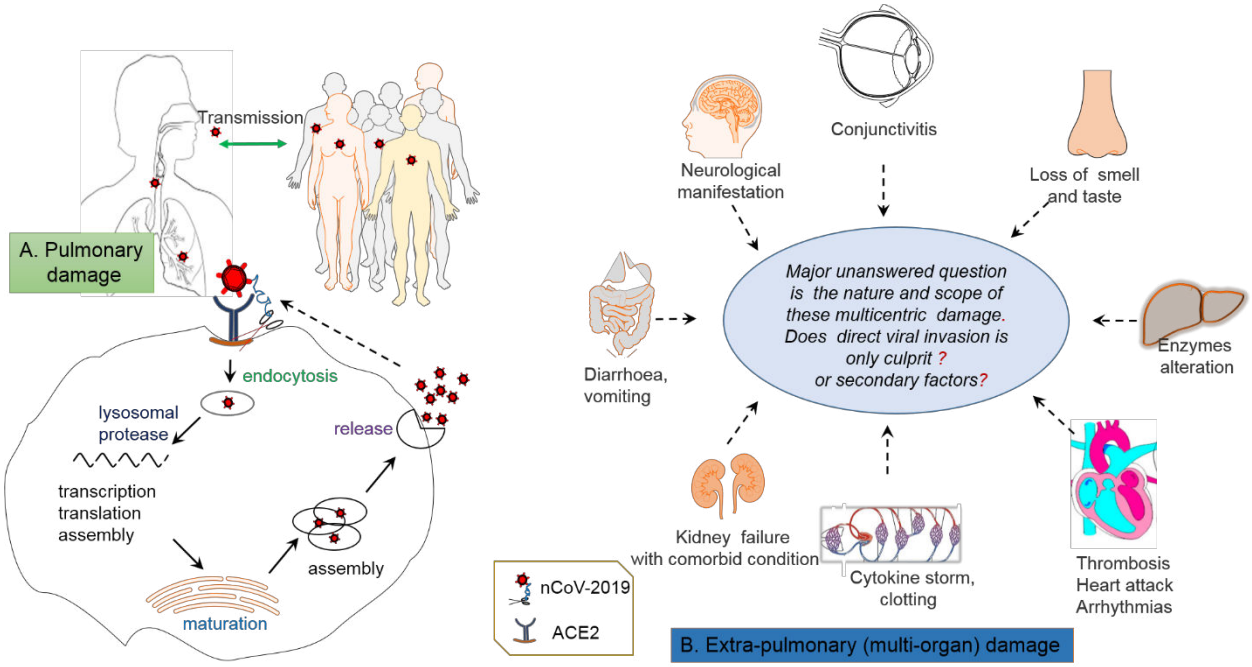

Figure 1: Life cycle and targets of nCoV-2019: The ACE2 acts as a key factor for the recognition and entry of the nCoV-2019 virus. The nCoV-2019 enters the human through the nose/throat and binds to ACE2 with help of the S1 subunit of its spike protein, fuses down the membrane using the S2 subunit. Once it enters the cells, it captures the host immune system by invading and infecting new cells. It attacks the lungs primarily however not limited to pulmonary manifestation. It damages other ACE2-rich target organs.

3. Metabolic link of COVID-19:

COVID-19 patients with metabolic comorbidity have shown more severe respiratory distress with increased mortality[11,12] and even higher than seasonal respiratory disease[13]. Moreover, the ACE2 polymorphism which is closely associated with metabolic illnesses also plays important role in predisposing these individuals toward COVID-19 infection[4]. However, the molecular mechanism behind this is poorly known and further studies are strongly required.

3.1. ACE2 vs. diabetes pathophysiology: Factors regulating ACE2 level.

The molecular connection between diabetes and ACE2 is well-known[14]. The Basal level of ACE2, which maintains homeostasis (Fig-2A) gets decreased in diabetes (Fig-2B) and becomes more dysregulated during the chronic stage[14]. A significantly enhanced expression of ACE2 was marked in 700 lung tissue from COVID-19 patients with various comorbidities[15].

3.1. A. Type 1 diabetes: NOD and Akita model (hyperglycemia and hypoinsulinemia): ACE2 activity and expression. Serum ACE2 activity was seen to increase in the NOD and AKITA diabetic model acutely and chronically whereas, insulin administration significantly decreased ACE2 activity[16] [17]. Pancreatic ACE2 activity was increased in type 1 diabetic mice models. ACE2 enzyme activity

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was significantly increased in the renal cortex from both early and late-stage type 1 diabetic mice as compared to non-diabetic controls. Overall, in the Type 1 diabetic mice model, blood glucose levels positively correlated with soluble ACE2 activity. However, the membrane-bound form of ACE2 is inversely correlated with hyperglycemia (Table 1). The membrane-bound ACE2 expression is enhanced in an organ-specific manner.

Table 1: Organ-specific regulation of ACE2 expression and activity evident from in-vivo studies.

	Serum/urine		Lungs		Renal	
	W/O Insulin treatment	**After Insulin administration**	**W/O Insulin treatment**	**After Insulin administration**	**W/O Insulin treatment**	**After Insulin administration**
ACE2(Activity)	Increases	Decreased	No changed	Increased	Increased	**Decreased**
ACE2/ACE activity	Increases	Decreased	Decreased in later stage only	Increased	-	**-**
ACE2 expression	Increases	Decreased	Increases	Decreased	Increases	**Decreased**

3.1. B. Type 2 diabetes (hyperinsulinemia and insulin resistance):

Signaling cross-talk between insulin and Ang-(1–7): Remarkably, ACE2 has emerged as an important putative target and key receptor for the spike glycoprotein of nCoV-2019[6]. The role of ACE2 took center stage in the COVID-19 outbreak and is thus a major area of interest to target COVID-19. ACE2 is a membrane glycoprotein expressed constitutively throughout the epithelial cells of lungs, kidneys, and blood vessels that cleaves Ang II to form Ang-(1–7). The anti-inflammatory effect of Ang-(1–7) protects metabolically targets organs by exerting anti-inflammation, antioxidant, vasodilator, and antifibrosis effects[18]. Insulin and Ang-(1–7) have some common signaling crosstalk which plays a significant role in maintaining a normal physiological state. ACE2 level is decreased in T2DM and gestational diabetic patients, which in turn, results in lower levels of Ang-(1–7) compared with healthy individuals[19]. Interestingly, Glucose intolerance and reduced first-phase insulin secretion have been described from ACE2-deficient mice, suggesting a potential role of ACE2 in the development of T2DM[20,21]. Loss of ACE2 in the pancreas contributes to, hyperglycemia, hyperinsulinemia, and β-cell dysfunction in *db/db* diabetic mice[16]. Mice infused with Ang2 exhibited hyperglycemia, hyperinsulinemia with impaired glucose-stimulated insulin

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secretion (GSIS), and adenoviral-mediated ACE2 overexpression (which resorted ACE2) rescued from these pathological states[22]. Loss of ACE2 in the pancreas contributes to β-cell dysfunction and hyperglycemia and the mechanism is thought to be the increased cleavage of ACE2[23]. Some results have suggested that ADAM17 is upregulated in *db/db* diabetic mice. ADAM17 is responsible for the shedding of several transmembrane proteins, including ACE2, and is well known to cleave ectodomain ACE2 and bring it to circulation[23]. ADAM17, a metalloprotease found to be increased in diabetes, CVS, and hypertension[17,23]. A decrease in ACE2 and an increase in ADAM17-mediated shedding activity have been observed with the progression of T2DM suggesting the importance of this mechanism in the disease[21]. On the other hand, insulin increases ACE2 expression in some insulin-sensitive cells (such as podocytes consisting of functionally active local renin-angiotensin system). However, prolonged insulin treatment fails to increase ACE2 expression (transition from insulin-sensitive state to insulin resistance state.[24] However, so far, it is not known how insulin increase

ACE2 expression? Does it bind to ACE2, or increase its stability? Some secondary factors upregulated (as a result of impaired cellular signaling) during the transition from an insulin-sensitive state to an insulin-resistant state may retard the effect of insulin and thereby prevent its action. Micro-albuminuria is an example of an independent risk factor for such pathogenesis as we can see albumin strongly oppose the ACE2 increasing capacity of insulin [24,25] (which is usually found during an insulin resistance state). The ACE2 is found to be protective in the insulin-resistant state as it enhances the phosphorylation level of AKT (Ser473), a surrogate marker for insulin sensitivity in-vivo and in-vitro[26]. Ang-(1–7) also increases the phosphorylation of GSK-3β. It has been shown recently that Ang-(1–7) also plays an important role in maintaining fast and fed state glucose homeostasis through maintaining an equilibrium between Akt and FOXO1 activation. Ang-(1–7) is also reported to enhance the delivery of insulin to the peripheral target and potentiate the action of insulin[18]. Most of the prescribed anti-diabetic medications cause an increase in ACE2 level and thus exert a protective/beneficial effect[27,28], which in turn facilitates SARS-to enter the host, and make myriad copies to invade new cells and invade the cell's machinery (Fig-2C-D).

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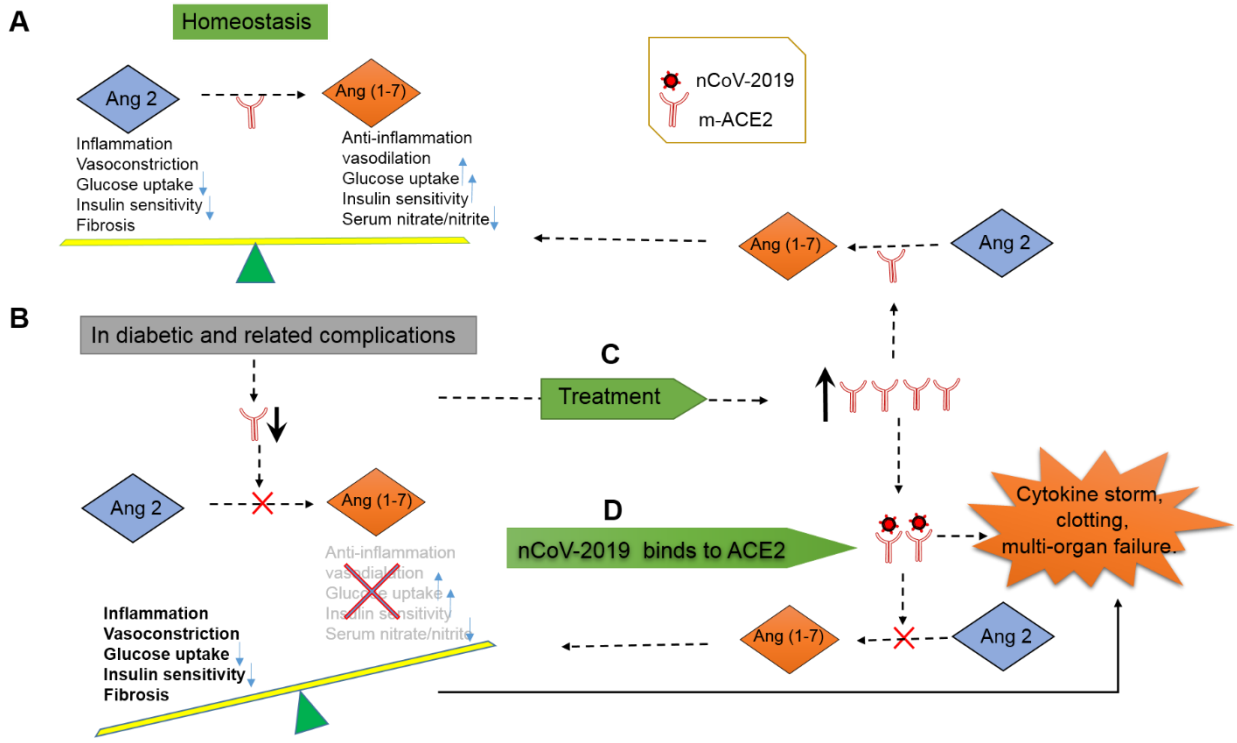

Figure 2: Metabolic link between COVID-19 and diabetes: ACE2 acts as a two-way sword: A. Basal ACE2 expression maintain cell homeostasis. **B.** when diabetes and associated complications such as hypertension progress, ACE2 expression starts decreasing. **C.** The most important goal in such illness is to maintain ACE2 level and the medication boosts the ACE2 level which is protective in such patients**. D**. Contrarily increased ACE2 (which has emerged as a receptor for nCoV-2019) encourages nCoV-2019 to bind ACE2 more and more. The metabolic illness demands more ACE2 (is protective in insulin resistance and related state) which puts individuals more susceptible to COVID-19 infection which in turn again makes the metabolic disease more severe due to cytokine storm).

4. Major challenges and future directions: Multiple endeavors to develop a vaccine against coronavirus disease 2019 (COVID-19) are in progress. A combination of FDA-approved drugs has been repurposed to treat COVID-19[29], however, to date, no single drug is available which can be truly labeled for COVID-19. Co-existence of metabolic syndrome or metabolic diseases with COVID-19 is like a double-edged sword as anti-diabetes and related complications (insulin resistance, hyperinsulinemia, hypertension, CVS) therapeutics force to enhance ACE2 level to exert its protective effects, which in turn provides more chance to the virus for its entry to cells and aggravate the condition by causing cytokine storm (releasing major proinflammatory markers such as *TNFα and IL1*β*, and IL6* and making metabolic illness more severe), multiple organ damage and even complete organ failure.

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In a recent report Zhu et al., 2020 performed a retrospective longitudinal, multi-centered study from a cohort of 9,663 confirmed COVID-19 cases on the association between plasma glucose levels and clinical outcomes in COVID-19 patients with T2DM. Their data suggested a strong association between diabetic status and higher mortality rates in patients with COVID-19 and pre-existing T2DM versus non-diabetic subjects with COVID-19[30]. Interestingly, their study also indicated that well-controlled glycemia was associated with a markedly improved outcome in patients with COVID-19 and pre-existing T2DM[30]. As a reliable COVID-19 vaccine is unlikely to be available before the maximal infection of COVID-19 has occurred, it is essential to establish therapeutics for individuals at high risk of the disease, particularly with T2DM and obesity. So, this forces us to think about the proper therapeutic intervention and especially in a situation where prediabetic diabetic and metabolic illness is at most high prevalence; It is fact that many patients with T2DM are obese and obesity and T2DM patients are a risk factor for severe COVID-19 infection and have impaired immune response. T2DM is often treated with angiotensin-converting enzyme (ACE) inhibitors. Coronavirus binds to target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed in the epithelial cells in the lungs, blood vessels, and the intestine. In patients treated with ACE and angiotensin II receptor blockers, the expression of ACE2 is increased. Therefore, it has been suggested that ACE2 expression may be increased in T2DM patients with hypertension and obesity, which could facilitate infection with COVID-19 and increase the risk of severe disease and fatality. For patients with COVID-19 and pre-existing T2DM, a key challenge for clinicians is to improve glycemic management. Thus, detailed analyses of data from such patients are needed that link plasma glucose levels with clinical outcomes, including mortality.

We propose to design an anti-diabetic and (or) small molecule capable of reducing diabetes-associated adverse events [31] that can also bind and interfere with the binding affinity between ACE2-Spike protein, to mitigate the viral infection (Fig-3) and with the following properties may be useful as a COVID-19 antidote: **i**. Small molecules/therapeutics compete with virus spike protein to bind with ACE2 as a result less virus will find its real receptor (Fig-3). **ii**. Small molecules will induce ACE2 expression and also increase soluble ACE2 levels. Soluble ACE2 can sequester the virus spike protein and neutralizes the virus like an antibody, so the virus will not be able to find its actual receptor. With fewer viruses, it will slow down viral infection and improve the disease because the virus cannot penetrate and infect the cells

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(Fig-3). iii. The anti-inflammatory, antioxidant, and anti-diabetic effects of the compound will act synergistically to combat the viral infection, specifically in those who are associated with metabolic comorbidities (Fig-3).

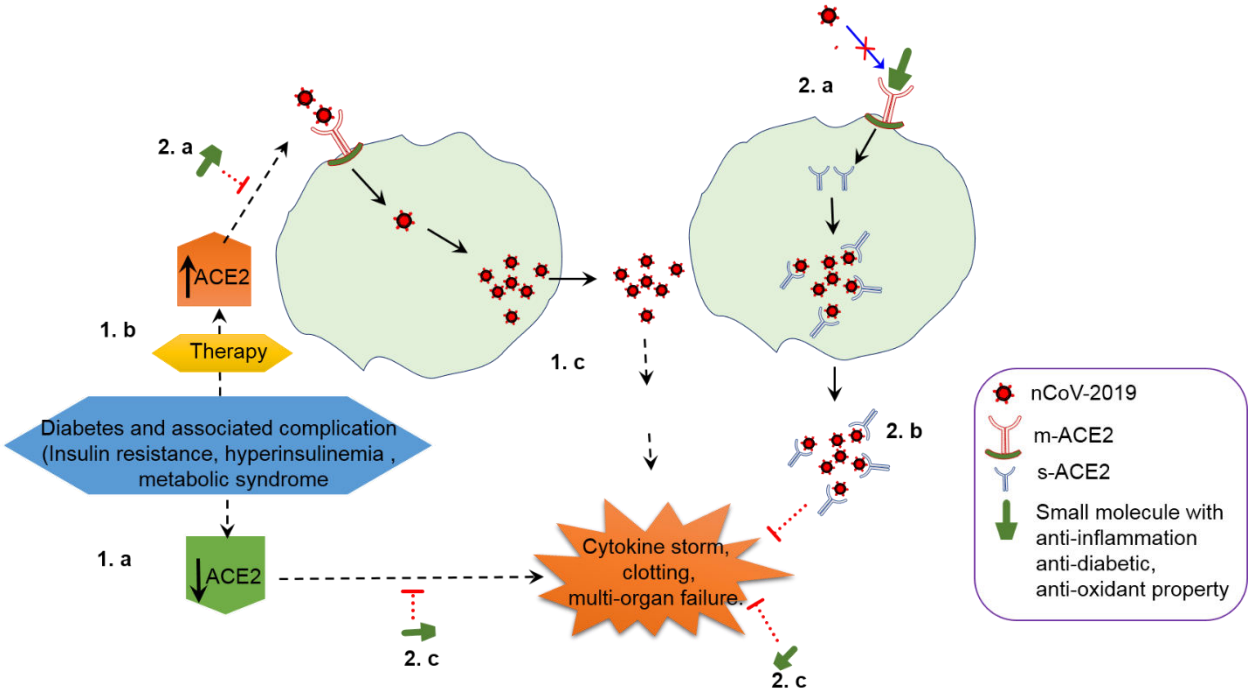

Figure 3: Possible targets to retard the nCoV-2019 extracellularly and mitigate its intracellular effect. 1. ACE2 expression is downregulated in diabetes and associated complications such as hypertension. **1**. b the therapy target is to enhance ACE2 but this in turn provides the chance to coronavirus to find its more receptor and leads to organ failure **(1.c). 2a.** Small molecule if bind with ACE2, can compete with spike protein as a result less virus will find its real receptor. **2. b** Small molecules will increase soluble ACE2 levels which can sequester the virus spike protein and soak up the virus like a neutralizing antibody. This would slow the virus to replicate and thus lesser cell will be infected. It can also increase the clearance of virus. **2c**. The anti-inflammatory, antioxidant and anti-diabetic effect of compound will act synergistically to combat the viral infection specifically in those who are associated with metabolic comorbidities.

References

1. Lu, H., Stratton, C. W. & Tang, Y. W. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *Journal of Medical Virology* **92**, 401–402 (2020).

2. WHO | World Health Organization. Available at: https://www.who.int/. (Accessed: 28th April 2020)

3. Zhao, J. *et al.* Relationship between the ABO Blood Group and the COVID-19 Susceptibility. *medRxiv* 2020.03.11.20031096 (2020). doi:10.1101/2020.03.11.20031096

4. Fang, L., Karakiulakis, G. & Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet Respiratory Medicine* **8**, e21 (2020).

5. Walls, A. C. *et al.* Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 8, Dec 2022

181, 281-292.e6 (2020).

6. Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).

7. Cai, G. Tobacco-Use Disparity in Gene Expression of ACE2, the Receptor of 2019-nCov. (2020). doi:10.20944/PREPRINTS202002.0051.V1

8. Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **579**, 270–273 (2020).

9. Hamming, I. *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* **203**, 631–637 (2004).

10. Li, F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annu. Rev. Virol.* **3**, 237–261 (2016).

11. Guan, W. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* NEJMoa2002032 (2020). doi:10.1056/NEJMoa2002032

12. Wu, C. *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern. Med.* (2020). doi:10.1001/jamainternmed.2020.0994

13. Fedson, D. S., Opal, S. M. & Rordam, O. M. Hiding in plain sight: An approach to treating patients with severe covid-19 infection. *MBio* **11**, (2020).

14. Batlle, D., Soler, M. J. & Ye, M. ACE2 and diabetes: ACE of ACEs? *Diabetes* **59**, 2994–2996 (2010).

15. Pinto, B. G. *et al.* ACE2 Expression is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19. *medRxiv* 2020.03.21.20040261 (2020). doi:10.1101/2020.03.21.20040261

16. Riera, M. *et al.* Effect of insulin on ACE2 activity and kidney function in the non-obese diabetic mouse. *PLoS One* **9**, (2014).

17. Salem, E. S. B., Grobe, N. & Elased, K. M. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. *Am. J. Physiol. Physiol.* **306**, F629–F639 (2014).

18. Dominici, F. P., Burghi, V., Muñoz, M. C. & Giani, J. F. Modulation of the action of insulin by angiotensin-(1-7). *Clinical Science* **126**, 613–630 (2014).

19. Nogueira, A. I. *et al.* The pregnancy-induced increase of plasma angiotensin-(1-7) is blunted in

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 8, Dec 2022

gestational diabetes. *Regul. Pept.* **141**, 55–60 (2007).

20. Bernardi, S. *et al.* ACE2 deficiency shifts energy metabolism towards glucose utilization. *Metabolism.* **64**, 406–415 (2015).

21. Chhabra, K. H., Chodavarapu, H. & Lazartigues, E. Angiotensin converting enzyme 2: A new important player in the regulation of glycemia. *IUBMB Life* **65**, 731–738 (2013).

22. Bindom, S. M., Hans, C. P., Xia, H., Boulares, A. H. & Lazartigues, E. Angiotensin I-converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice. *Diabetes* **59**, 2540–2548 (2010).

23. Pedersen, K. B., Chodavarapu, H., Porretta, C., Robinson, L. K. & Lazartigues, E. Dynamics of ADAM17-mediated shedding of ACE2 applied to pancreatic islets of male db/db mice. *Endocrinology* **156**, 4411–4425 (2015).

24. Márquez, E., Riera, M., Pascual, J. & Soler, M. J. Albumin inhibits the insulin-mediated ACE2 increase in cultured podocytes. *Am. J. Physiol. - Ren. Physiol.* **306**, (2014).

25. Park, S. E. *et al.* High urinary ACE2 concentrations are associated with severity of glucose intolerance and microalbuminuria. *Eur. J. Endocrinol.* **168**, 203–210 (2013).

26. Schlessinger, J. Cell signaling by receptor tyrosine kinases. *Cell* **103**, 211–225 (2000).

27. Jearath, V., Vashisht, R., Rustagi, V., Raina, S. & Sharma, R. Pioglitazone-induced congestive heart failure and pulmonary edema in a patient with preserved ejection fraction. *J. Pharmacol. Pharmacother.* **7**, 41–43 (2016).

28. Romaní-Pérez, M. *et al.* Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. *Endocrinology* **156**, 3559–3569 (2015).

29. Choubey, A., Dehury, B., Kumar, S., Medhi, B. & Mondal, P. Naltrexone a potential therapeutic candidate for COVID-19. *J. Biomol. Struct. Dyn.* 1–8 (2020). doi:10.1080/07391102.2020.1820379

30. Zhu, L. *et al.* Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* (2020). doi:10.1016/j.cmet.2020.04.021

31. Choubey, A. *et al.* Low dose naltrexone rescues inflammation and insulin resistance associated with hyperinsulinemia. *J. Biol. Chem.* jbc.RA120.013484 (2020). doi:10.1074/jbc.ra120.013484