Biomedical Research and Therapy 2023, 10(9):5876-5883

Open Access Full Text Article

Review

Endocrine-disrupting pesticides and SARS-CoV-2 infection: Role of ACE2, TMPRSS2 and CD147

Swati Dixit[1], Haseeb Ahsan[2,*], Fahim Halim Khan[1,*]

Use your smartphone to scan this QR code and download this article

ABSTRACT

COVID-19 is a global pandemic caused by severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2). The three main receptors used by SARS-CoV-2 to bind and gain entry into human cells are ACE, TMPRSS2, and CD147. These molecular factors have crucial roles in human metabolism and homeostasis, but the upregulation of these factors causes severe diseases such as myocarditis, prostate cancer, and other endocrine-related cancers. Studies have found that once humans come into contact with SARS-CoV-2, the chances of being affected by such disorders increase; indeed, infection with the virus is associated with increased morbidity and mortality from heart attacks and pulmonary inflammation. Notably, exposure to some pesticides, such as chlorpyrifos, cypermethrin, and imidacloprid, which are identified as potential endocrine disruptors, causes such disorders by interfering with hormonal signaling pathways, such as the insulin-glucagon pathway and the thyroid pathway. This review focuses on the potential role of pesticides in exacerbating the comorbidities linked with SARS-CoV-2 and their effect on the molecular factors associated with SARS-CoV-2. Understanding the potential therapeutic implications of this link between SARS-CoV-2 severity and pesticides requires further clinical trials and investigations.

Key words: ACE2, cancer, CD147, endocrine disruptors, Pesticides, SARS-CoV-2, TMPRSS2

[1]*Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, India*

[2]*Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India*

Correspondence

Haseeb Ahsan, Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India

Email: drhahsan@gmail.com

Correspondence

Fahim Halim Khan, Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, India

Email: fahimhkhan@rediffmail.com

History

- Received: Jul 31, 2023
- Accepted: Aug 26, 2023
- Published Online: Sep 30, 2023

DOI : 10.15419/bmrat.v10i9.829

Check for updates

INTRODUCTION

The year 2019 witnessed one of the major catastrophes of the world. Spreading globally, the novel coronavirus has become one of the greatest threats to humankind. This coronavirus belongs to the severe acute respiratory syndrome coronavirus (SARS-CoV) family[1]. First identified following an outbreak in 2004[2] in Yunnan, China, SARS is responsible for multiple respiratory diseases such as the common cold, bronchitis, and pneumonia caused by severe acute respiratory syndrome coronavirus (SARS-CoV), which also caused the viral pandemic outbreak in 2019 (COVID-19)[3]. Owing to the high nucleotide substitution and recombination capacity of coronaviruses, SARS-CoV-2 is still mutating and evolving rapidly[2,4]. The severe outbreak of the novel strain SARS-CoV-2 in December 2019 in Wuhan Province of China caused a global breakdown in the economy while still posing a threat to human health, leading to unpredictable disastrous consequences[5]. SARS-CoVs are generally enveloped viruses with a single-stranded RNA genome[6]. The International Committee for Taxonomy of Viruses has classified the human coronavirus under the *Coronaviridae* family, which is genotypically and serologically further divided into four major genera: alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV[2]. Before the emergence of human coronavirus, there was evidence for the presence and harboring of coronavirus in various animals, such as bovine coronavirus (BCoV) and feline infectious peritonitis virus (FIPV)[7]. Over time, the parallel development of poultry farming and urbanization, and the frequent close contact of animals with one another and their exposure to humans contributed to the evolution and transmission of coronavirus in other species, such as bats[8,9]. Direct contact of humans with these coronavirus-harboring bats in 2019 has been suggested as a possible mode of transmission of the virus in humans[10]. Since then, SARS-CoV, which causes COVID-19, has affected many countries globally[11]. SARS-CoV-2 relies on ACE2, TMPRSS2, and CD147 to gain entry into human cells (**Figure 1**)[12]. ACE2, TMPRSS2, and CD147 receptors are present on the cells of various organs[13] and, by attaching itself to these receptors through various mechanisms, SARS-CoV-2 is able to enter various organs of the human body[14].

SARS-CoV-2 is composed of a phosphorylated nucleocapsid (N) protein containing genomic RNA[5]. This core unit is packed by a phospholipid bilayer envelope to form particles varying in shape and size ranging between 80-120 nm[15]. The characteristic feature of this assembly is characterized by sharp projections

BioMedPress The Open Access Publisher

Cite this article : Dixit S, Ahsan H, Khan F H. **Endocrine-disrupting pesticides and SARS-CoV-2 infection: Role of ACE2, TMPRSS2 and CD147**. *Biomed. Res. Ther.* 2023; 10(9):5876-5883.

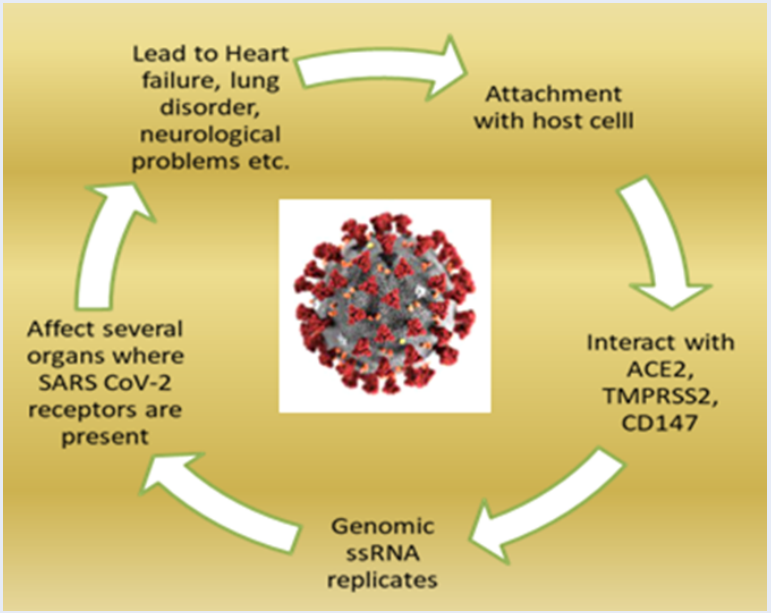

Figure 1: **A representation of mechanism of SARS-CoV-2 interacting with host factors ACE2, TMPRSS2 and CD147 leading to organ dysfunction. Abbreviations**: **ACE2**: Angiotensin-Converting Enyzme 2; **TMPRSS2**: Transmembrane Serine Protease 2; **CD147**: Cluster of Differentiation 147

known as spike or spike proteins (S) present on the outer surface[16]. Regarding its protein composition, SARS-CoV-2 is composed of four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins[1]. Only three viral proteins, S, E, and M, are embedded in the viral envelope, while the N protein is located in the core of the virus bound to the viral genomic RNA[17]. The S protein is a glycoprotein assembled as a trimeric unit and mediates receptor binding and membrane fusion, allowing the penetration and entry of the virus into host cells[18]. The genetic composition of SARS-CoV-2 is nonsegmented plus-sense single-stranded 26-31 kb RNA with varied G+C content (32%–43%)[19]. The genome composition is: 5′-leader-UTR-replicase/transcriptase-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail[20]. The 5′UTR and 3′UTR are involved in RNA-RNA interactions during the binding of viruses with other cellular proteins[21].

The virus assembly consists of 4 structural proteins: nucleocapsid (N), envelope (E), spike (S), and membrane (M) protein[1]. After the synthesis of the SARS-CoV-2 structural proteins and genomic RNA at the replication site, an unknown mechanism translocates these entities at the ER-Golgi intermediate compartment (ERGIC) for the assembly of the virus and budding[22], during which the structural proteins become embedded in the outer structure, while the N protein packs itself along with the genomic RNA, making up the virion[23]. The E and M proteins of the virus assembly help in budding, whereas the S protein is involved in the initial host-virus interaction[24]. The first step in the interaction is attachment of the virus to the cell membrane of the host, which is regulated by the S glycoprotein[25]. The S protein organizes itself in an identical trimeric manner[23]. Multiple copies of this structure are embedded in the viral envelope membrane, and this glycoprotein moiety is recognized by host cell receptors[26]. During biosynthesis and maturation in the infected cell, the recognition phase occurs, at which point this trimeric unit is usually cleaved from the viral structure by the protease furin from the Golgi apparatus[27], leaving only two subunits behind, *i.e.*, S1 and S2. The S1 subunit is recognized by angiotensin-converting enzyme (ACE2) and binds to it[1]. After budding, the virus moves to the ERGIC lumen and reaches the plasma membrane, traveling through secretory pathways where the S2 subunit fuses with the membrane mediated by a fusion peptide (FP)[28].

INVOLVEMENT OF SARS-COV-2-ASSOCIATED MOLECULAR FACTORS

ACE2

Angiotensin-converting enzyme 2 (ACE2) is an enzyme found in various locations in the human

body[29]. It is mostly found attached to the cell membranes of the heart, intestines, gall bladder, testes, and kidney[30,31]. It exists in two forms: membrane-bound (mACE2) and soluble (sACE2)[32], which make up the renin-angiotensin-aldosterone system (RAAS) that maintains the body's blood pressure[33]. mACE2 acts on the enzyme ADAM17, cleaving its extracellular domain to create sACE2, which catalyzes the hydrolysis of angiotensin II into angiotensin[34]. Angiotensin II is a vasoconstrictor peptide angiotensin (1-7)[35] and induces vasodilation after binding with MasR receptors, hence lowering blood pressure and antagonizing the effects of ACE2[36]. This phenomenon is a potential target for drugs that are used in cardiovascular disease treatment[37]. ACE2 (membrane-bound) is also functionally known as the receptor for the spike glycoprotein of the human coronavirus SARS-CoV-2[38]. Recognizing this interaction of ACE2 with SARS-CoV-2 has accelerated some novel therapeutic approaches to reduce ACE2 expression or block the enzyme to prevent the cellular entry of SARS-CoV-2 in the kidney, heart, lung, and brain, where ACE2 is expressed[39].

TMPRSS2

Transmembrane serine protease 2 (TMPRSS2) is a cell surface protein located in endothelial cells lining the heart, liver, respiratory, and digestive tracts[40]. As a serine protease, it is functionally involved in the cleavage of peptide bonds of proteins that have serine as the nucleophilic amino acid within the active site[41]. It is encoded by the *TMPRSS2* gene and is a member of the TMPRSS family of transmembrane proteins exhibiting serine protease activity[42]. The protease activity of this protein is used by SARS-CoV-2 to enter cells[43]. Mutations of the *TMPRSS2* gene can lead to prostate cancer. The overexpression of TMPRSS2 and prostate carcinogenesis involves the interplay of the transcription factors ERG and ETV1[44,45]. Their enhanced expression stimulates the downregulation of androgen receptor signaling[46]. The protease activity of TMPRSS2 is exploited by SARS-CoV-2 to gain entry into the heart, liver, and respiratory cells[40]. The S1 and S2 subunits of the virus are cleaved by the proteolytic activity of TMPRSS2[29].

CD147

In addition to ACE2 and TMPRSS2, another receptor, CD147, is also responsible for SARS-CoV-2 entry into the epithelial cell lining[12]. CD147 is a transmembrane receptor that forms a transmembrane supramolecular complex and interacts with several extracellular and intracellular factors[47]. CD147 suppresses NOD2 and the gamma-secretase protein complex[48]. NOD2 is part of the innate immune system, and gamma-secretase is responsible for the cleavage of beta-amyloid precursor from the plasma membrane[17]. Owing to its diverse interactions, CD147 has crucial roles in cell metabolism, motility, and activation[49]. The initiation of programmed cell death, lymphopenia, and cellular overactivation is suggested to occur as a result of the CD147-SARS-CoV-2 interaction[50]. Cyclophilins A and B are the two main extracellular ligands of CD147 that are recognized by the nucleocapsid protein and then bind with the spike protein of SARS-CoV-2[49]. The presence of three Asn glycosylation sites in this receptor is also suggested to bind with the glycosylated spike protein of SARS-CoV-2[51,52].

EFFECT OF PESTICIDE EXPOSURE ON ACE2, TMPRSS2 AND CD147

Endocrine disruptors (EDs) are chemicals that disturb normal human body metabolism by interfering with hormones in the endocrine system[53]. These chemicals are known to cause developmental, neurological, reproductive, and immunological disorders[54] and are present in plasticware, detergents, cosmetics, and pesticides[55]. This review focuses on pesticides as endocrine disruptors. Human exposure to such chemicals can cause cardiometabolic diseases, hypertension, diabetes, and other endocrine-related cancers[56]. With the expansion of SARS-CoV-2 worldwide, the risk of severe diseases such as asthma, cancer, cardiovascular disease, hypertension, diabetes[57], and obesity also increased, suggesting a possible connection of these chemicals with SARS-CoV-2.

Although these relationships have not yet been explored to any great extent, several studies hint at the possible involvement of ED chemicals in SARS-CoV-2 susceptibility. Pesticides such as chlorpyrifos, deltamethrin, cypermethrin, and imidacloprid have been identified as possible endocrine disruptors[58]. Using computational approaches, some of the pathways have been identified as potential targets of endocrine disruptors that contribute to COVID-19 severity[59]. These signaling pathways include TNF[60], insulin resistance, endocrine resistance, MAPK[61], IL-17, and prolactin pathways[62]. Ivermectin is an insecticide that has been identified to show mosquitocidal effects. A study by Lehrer *et al.* showed the interaction of ivermectin binding with the SARS-CoV-2 spike-RBD-ACE2 complex[63]. A study of cotton aphids exposed to omethoate, an insecticide, was

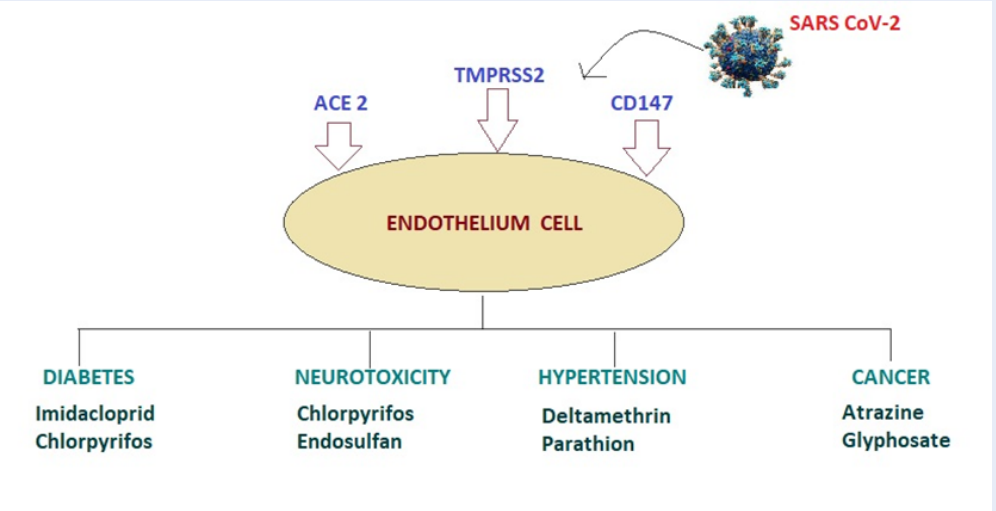

Figure 2: **The relation between pesticides induced metabolic disorders associated with SARS-CoV-2 severity and the involvement of some receptors (ACE2, TMPRSS2, CD147). Abbreviations**: **ACE2**: Angiotensin-Converting Enyzme 2; **TMPRSS2**: Transmembrane Serine Protease 2; **CD147**: Cluster of Differentiation 147

found to downregulate ACE2 mRNA[64]. The insecticide methamidophos has been shown to affect ACE2 levels in *Oomyzus sokolowskii*[65], while some organophosphates have been found to affect ACE2 via RNA interference (RNAi)[66].

Pesticides are a broad range of chemicals widely used in domestic settings and agriculture[67]. Exposure to pesticides such as organochlorines, pyrethroids, organophosphates, and carbamates results in disturbances in the normal hormonal functioning of the human body[68]. Therefore, these chemicals are also classified as endocrine disruptors[67]. Exposure to these chemicals with human mitochondrial metabolic factors such as ACE2, TMRPSS2, and CD147 also opens the door for SARS-CoV-2 involvement[69](**Figure 2**). The novel beta-SARS-CoV-2 caused the global health crisis COVID-19[2]. When the virus comes into contact with its living host, it targets ACE2, TMPRSS2, and CD147[70]. Environmental pollutants can have a wide range of effects on human metabolism. It has been reported that particulate matter from smoking or factories can increase SARS-CoV-2 severity[71], but it is unclear whether these pesticides can make organs more susceptible to SARS-CoV-2[72]. Studies have revealed that activation of the IL-8/CXCR1/2 pathway in lung fibroblasts is triggered by pesticides and air pollutants[62], resulting in upregulation of ACE2 and TMPRSS2 levels, thereby increasing the risk of SARS-CoV-2 infection. The upregulation was prevented by blocking the IL-8/CXCR1/2 pathway[73]. Clinical trials are required to determine whether pesticides are linked with SARS-CoV-2 severity and, if yes, it is important to directly or indirectly uncover the underlying mechanisms and pathways[74]. Given the importance of TMPRSS2 in SARS-CoV-2 infection, a number of studies have considered potential therapeutic approaches that might target this receptor. Certain selective bioactive compounds, from organisms such as *P. grandiflorus* , show promise as an alternative treatment option against SARS-CoV-2 infections by targeting TMPRSS2[75]. Similarly, designing peptide-mimicking compounds that can inhibit TMPRSS2 activity is another possible approach[76]. α-Terthienyl, a new-generation insecticide, downregulates TMPRSS2 by reducing its mRNA and protein expression[77] but increases the expression of p27, a tumor suppressor gene[78]. Some anti-CD147 drugs, such as meplazumab, inhibit SARS-CoV-2 in patients with COVID-19 pneumonia[79]. Another approach is the truncation of the cytoplasmic tail of CD147 to prevent the entry of SARS-CoV-2[80]. As discussed, some environmental toxicants (pesticides) are known to modulate ACE2, TMPRSS2, and CD147 expression thus, further preclinical studies and clinical trials are required to assess inhibitory compounds against these toxicants[81].

CONCLUSION

The receptors ACE2, TMPRSS2 and CD147 are the main entry for the SARS-CoV-2 in humans. These molecular factors play a crucial role in human metabolism and homeostatis but their overex-

pression and upregulation leads to various pathophysiological conditions. The endocrine disrupting pesticides such as chlorpyripos, cypermethrin, imidacloprid modulate the expression of ACE2, TMPRSS2 and CD147. The COVID-19 is associated with severe inflammatory conditions leading to cardiovascular and pulmonary pathologies. Hence, the exposure of these endocrine disrupting pesticides will increase the comorbidities associated with SARS-CoV-2 infection by interfering with the hormonal signaling pathways. Hence, the present review article explores the link between pesticide exposure and endocrine receptors associated with SARS-CoV-2 infection.

ABBREVIATIONS

ACE2: angiotensin onverting enzyme 2; **CD147**: cluster of differentiation 147; **COVID-19**: coronavirus disease-2019; **ED**: endocrine disrupting/disruptors; **SARS-CoV-2**: severe acute respiratory syndrome coronavirus 2; **TMPRSS2**: transmembrane serine protease 2

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

SD: data collection; analysis and interpretation of results; draft manuscript preparation. HA: study conception and design; analysis and interpretation of results; draft manuscript preparation; correction and proofreading of manuscript. FHK: study conception and design; analysis and interpretation of results; All authors approved the final version of the manuscript for submission.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nature Reviews Molecular Cell Biology. 2022;23(1):3–20. PMID: 34611326. Available from: https://doi.org/10.1038/s41580-021-00418-x.
2. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;2020(579):265–580:E7. Available from: https://doi.org/10.1038/s41586-020-2008-3.
3. Pene F, Merlat A, Vabret A, Rozenberg F, Buzyn A, Dreyfus F. Coronavirus 229E-related pneumonia in immunocompromised patients. Clinical Infectious Diseases. 2003;37(7):929–32. PMID: 13130404. Available from: https://doi.org/10.1086/377612.
4. Vijgen L, Keyaerts E, Moës E, Maes P, Duson G, Ranst MV. Development of one-step, real-time, quantitative reverse transcriptase PCR assays for absolute quantitation of human coronaviruses OC43 and 229E. Journal of Clinical Microbiology. 2005;43(11):5452–6. PMID: 16272469. Available from: https://doi.org/10.1128/JCM.43.11.5452-5456.2005.
5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3. PMID: 32015507. Available from: https://doi.org/10.1038/s41586-020-2012-7.
6. Masters PS. The molecular biology of coronaviruses. Advances in Virus Research. 2006;66:193–292. PMID: 16877062. Available from: https://doi.org/10.1016/S0065-3527(06)66005-3.
7. Saif LJ. Animal coronaviruses: what can they teach us about the severe acute respiratory syndrome? Revue Scientifique et Technique (International Office of Epizootics). 2004;23(2):643–60. PMID: 15702725. Available from: https://doi.org/10.20506/rst.23.2.1513.
8. Xie J, Li Y, Shen X, Goh G, Zhu Y, Cui J, et al. Dampened STING-dependent interferon activation in bats. Cell Host & Microbe. 2018;23(3):P297–301.e4. PMID: 29478775. Available from: https://doi.org/10.1016/j.chom.2018.01.006.
9. Gouilh MA, Puechmaille SJ, Diancourt L, Vandenbogaert M, Serra-Cobo J, Roig ML, et al. SARS-CoV related Betacoronavirus and diverse Alphacoronavirus members found in western old-world. Virology. 2018;517:88–97. PMID: 29482919. Available from: https://doi.org/10.1016/j.virol.2018.01.014.
10. Banerjee A, Kulcsar K, Misra V, Frieman M, Mossman K. Bats and Coronaviruses. Viruses. 2019;11(1):41. PMID: 30634396. Available from: https://doi.org/10.3390/v11010041.
11. Kirtipal N, Bharadwaj S, Kang SG. From SARS to SARS-CoV-2, insights on structure, pathogenicity and immunity aspects of pandemic human coronaviruses. Infection, Genetics and Evolution. 2020;85:104502. PMID: 32798769. Available from: https://doi.org/10.1016/j.meegid.2020.104502.
12. Wang K, Chen W, Zhou YS, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv 2020:202020032014988345. 2020;Available from: https://doi.org/10.1101/2020.03.14.988345.
13. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581(7807):215–20. PMID: 32225176. Available from: https://doi.org/10.1038/s41586-020-2180-5.
14. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS- CoV-2 spike glycoprotein. Cell. 2020;181(2). PMID: 32155444. Available from: https://doi.org/10.1016/j.cell.2020.02.058.
15. Bárcena M, Oostergetel GT, Bartelink W, Faas FG, Verkleij A, Rottier PJ. Cryo-electron tomography of mouse hepatitis virus: insights into the structure of the coronavirion. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(2):582–7. PMID: 19124777. Available from: https://doi.org/10.1073/pnas.0805270106.

16. Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P. Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. Journal of Virology. 2006;80(16):7918–28. PMID: 16873249. Available from: https://doi.org/10.1128/JVI.00645-06.
17. Zhou S, Zhou H, Walian PJ, Jap BK. CD147 is a regulatory subunit of the gamma-secretase complex in Alzheimer's disease amyloid beta-peptide production. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(21):7499–504. PMID: 15890777. Available from: https://doi.org/10.1073/pnas.0502768102.
18. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. Journal of Virology. 2003;77(16):8801–11. PMID: 12885899. Available from: https://doi.org/10.1128/JVI.77.16.8801-8811.2003.
19. Yang H, Bartlam M, Rao Z. Drug design targeting the main protease, the Achilles' heel of coronaviruses. Current Pharmaceutical Design. 2006;12(35):4573–90. PMID: 17168763. Available from: https://doi.org/10.2174/138161206779010369.
20. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. Journal of Microbiology, Immunology and Infection. 2021;54(2):159–63. Available from: https://doi.org/10.1016/j.jmii.2020.03.022.
21. Yang D, Leibowitz JL. The structure and functions of coronavirus genomic 3' and 5' ends. Virus Research. 2015;206:120–33. PMID: 25736566. Available from: https://doi.org/10.1016/j.virusres.2015.02.025.
22. Stertz S, Reichelt M, Spiegel M, Kuri T, Martínez-Sobrido L, García-Sastre A. The intracellular sites of early replication and budding of SARS-coronavirus. Virology. 2007;361(2):304–15. PMID: 17210170. Available from: https://doi.org/10.1016/j.virol.2006.11.027.
23. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nature Reviews Microbiology. 2021;19(3):155–70. PMID: 33116300. Available from: https://doi.org/10.1038/s41579-020-00468-6.
24. Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, Lee WW. Ultrastructural characterization of SARS coronavirus. Emerging Infectious Diseases. 2004;10(2):320–6. PMID: 15030705. Available from: https://doi.org/10.3201/eid1002.030913.
25. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences of the United States of America. 2020;117(21):11727–34. PMID: 32376634. Available from: https://doi.org/10.1073/pnas.2003138117.
26. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virology Journal. 2019;16(1):69. PMID: 31133031. Available from: https://doi.org/10.1186/s12985-019-1182-0.
27. Hoffmann M, Kleine-Weber H, Pöhlmann S. Multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Molecular Cell. 2020;78(4). PMID: 32362314. Available from: https://doi.org/10.1016/j.molcel.2020.04.022.
28. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods in Molecular Biology (Clifton, NJ). 2015;1282:1–23. PMID: 25720466. Available from: https://doi.org/10.1007/978-1-4939-2438-7_1.
29. NCBI "Gene: ACE2, angiotensin I converting enzyme 2". National Center for Biotechnology Information (NCBI). U.S. National Library of Medicine. 2020-02-28; 2020.
30. Hikmet F, Méar L, Edvinsson AA, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. Molecular Systems Biology. 2020;16(7):e9610. PMID: 32715618. Available from: https://doi.org/10.15252/msb.20209610.
31. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology. 2004;203(2):631–7. PMID: 15141377. Available from: https://doi.org/10.1002/path.1570.
32. Diz DI, Garcia-Espinosa MA, Gegick S, Tommasi EN, Ferrario CM, Tallant EA. Injections of angiotensin-converting enzyme 2 inhibitor MLN4760 into nucleus tractus solitarii reduce baroreceptor reflex sensitivity for heart rate control in rats. Experimental Physiology. 2008;93(5):694–700. PMID: 18356558. Available from: https://doi.org/10.1113/expphysiol.2007.040261.
33. Dong B, Zhang C, Feng JB, Zhao YX, Li SY, Yang YP. Overexpression of ACE2 enhances plaque stability in a rabbit model of atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28(7):1270–6. PMID: 18403726. Available from: https://doi.org/10.1161/ATVBAHA.108.164715.
34. Ferrario CM, Jessup J, Gallagher PE, Averill DB, Brosnihan KB, Tallant EA. Effects of renin-angiotensin system blockade on renal angiotensin-(1-7) forming enzymes and receptors. Kidney International. 2005;68(5):2189–96. PMID: 16221218. Available from: https://doi.org/10.1111/j.1523-1755.2005.00675.x.
35. Hoffmann M, Kleine-Wever H, Kruger N, Muller M, Drotsten C, Pholhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry in target cells. Cell. 2020;181:1–10.
36. Garabelli PJ, Modrall JG, Penninger JM, Ferrario CM, Chappell MC. Distinct roles for angiotensin-converting enzyme 2 and carboxypeptidase A in the processing of angiotensins within the murine heart. Experimental Physiology. 2008;93(5):613–21. PMID: 18356559. Available from: https://doi.org/10.1113/expphysiol.2007.040246.
37. Jia HP, Look DC, Tan P, Shi L, Hickey M, Gakhar L. Ectodomain shedding of angiotensin converting enzyme 2 in human airway epithelia. American Journal of Physiology Lung Cellular and Molecular Physiology. 2009;297(1):84–96. PMID: 19411314. Available from: https://doi.org/10.1152/ajplung.00071.2009.
38. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Medicine. 2005;11(8):875–9. PMID: 16007097. Available from: https://doi.org/10.1038/nm1267.
39. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260–3. PMID: 32075877. Available from: https://doi.org/10.1126/science.abb2507.
40. Bertram S, Glowacka I, Blazejewska P, Soilleux E, Allen P, Danisch S. TMPRSS2 and TMPRSS4 facilitate trypsin-independent spread of influenza virus in Caco-2 cells. Journal of Virology. 2010;84(19):10016–25. PMID: 20631123. Available from: https://doi.org/10.1128/JVI.00239-10.
41. Thunders M, Delahunt B. Gene of the month: TMPRSS2 (transmembrane serine protease 2). Journal of Clinical Pathology. 2020;73(12):773–6. PMID: 32873700. Available from: https://doi.org/10.1136/jclinpath-2020-206987.
42. Gierer S, Bertram S, Kaup F, Wrensch F, Heurich A, Krämer-Kühl A. The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. Journal of Virology. 2013;87(10):5502–11. PMID: 23468491. Available from: https://doi.org/10.1128/JVI.00128-13.
43. Bossart KN, Wang LF, Flora MN, Chua KB, Lam SK, Eaton BT. Membrane fusion tropism and heterotypic functional activities of the Nipah virus and Hendra virus envelope glycoproteins. Journal of Virology. 2002;76(22):11186–98. PMID: 12388678. Available from: https://doi.org/10.1128/JVI.76.22.11186-11198.2002.
44. Winnes M, Lissbrant E, Damber JE, Stenman G. Molecular genetic analyses of the TMPRSS2-ERG and TMPRSS2-ETV1 gene fusions in 50 cases of prostate cancer. Oncology Reports. 2007;17(5):1033–6. PMID: 17390040. Available from: https:

//doi.org/10.3892/or.17.5.1033.
45. Beuzeboc P, Soulié M, Richaud P, Salomon L, Staerman F, Peyromaure M. [Fusion genes and prostate cancer. From discovery to prognosis and therapeutic perspectives]. Progres en Urologie. 2009;19(11):819–24. PMID: 19945666. Available from: https://doi.org/10.1016/j.purol.2009.06.002.
46. Yu J, Yu J, Mani RS, Cao Q, Brenner CJ, Cao X. An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. Cancer Cell. 2010;17(5):443–54. PMID: 20478527. Available from: https://doi.org/10.1016/j.ccr.2010.03.018.
47. Muramatsu T. Basigin (CD147), a multifunctional transmembrane glycoprotein with various binding partners. Journal of Biochemistry. 2016;159(5):481–90. PMID: 26684586. Available from: https://doi.org/10.1093/jb/mvv127.
48. Till A, Rosenstiel P, Bräutigam K, Sina C, Jacobs G, Oberg HH. A role for membrane-bound CD147 in NOD2-mediated recognition of bacterial cytoinvasion. Journal of Cell Science. 2008;121(Pt 4):487–95. PMID: 18256385. Available from: https://doi.org/10.1242/jcs.016980.
49. Radzikowska U, Ding M, Tan G, Zhakparov D, Peng Y, Wawrzyniak P. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy. 2020;75(11):2829–45. PMID: 32496587. Available from: https://doi.org/10.1111/all.14429.
50. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A. Clinical Characteristics of Covid-19 in New York City. The New England Journal of Medicine. 2020;382(24):2372–4. PMID: 32302078. Available from: https://doi.org/10.1056/NEJMc2010419.
51. Huang W, Luo WJ, Zhu P, Tang J, Yu XL, Cui HY. Modulation of CD147-induced matrix metalloproteinase activity: role of CD147 N-glycosylation. The Biochemical Journal. 2013;449(2):437–48. PMID: 23005037. Available from: https://doi.org/10.1042/BJ20120343.
52. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerging Microbes & Infections. 2020;9(1):601–4. PMID: 32178593. Available from: https://doi.org/10.1080/22221751.2020.1739565.
53. Dixit S, Zia MK, Siddiqui T, Ahsan H, Khan FH. Interaction of Human Alpha-2-Macroglobulin with Pesticide Aldicarb Using Spectroscopy and Molecular Docking. Protein and Peptide Letters. 2021;28(3):315–22. PMID: 32957873. Available from: https://doi.org/10.2174/0929866527666200921165834.
54. Mnif W, Hassine AI, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of endocrine disruptor pesticides: a review. International Journal of Environmental Research and Public Health. 2011;8(6):2265–303. PMID: 21776230. Available from: https://doi.org/10.3390/ijerph8062265.
55. Darbre PD. Chemical components of plastics as endocrine disruptors: overview and commentary. Birth Defects Research. 2020;112(17):1300–7. PMID: 32720473. Available from: https://doi.org/10.1002/bdr2.1778.
56. Zahra A, Sisu C, Silva E, Greca SCDA, Randeva HS, Chatha K. Is There a Link between Bisphenol A (BPA), a Key Endocrine Disruptor, and the Risk for SARS-CoV-2 Infection and Severe COVID-19? Journal of Clinical Medicine. 2020;9(10):3296. PMID: 33066495. Available from: https://doi.org/10.3390/jcm9103296.
57. Sandoval M, Nguyen DT, Vahidy FS, Graviss EA. Risk factors for severity of COVID-19 in hospital patients age 18-29 years. PLoS One. 2021;16(7):e0255544. PMID: 34329347. Available from: https://doi.org/10.1371/journal.pone.0255544.
58. Abdel-Razik RK, Mosallam EM, Hamed NA, Badawy ME, Abo-El-Saad MM. Testicular deficiency associated with exposure to cypermethrin, imidacloprid, and chlorpyrifos in adult rats. Environmental Toxicology and Pharmacology. 2021;87:103724. PMID: 34416397. Available from: https://doi.org/10.1016/j.etap.2021.103724.
59. Wu Q, Coumoul X, Grandjean P, Barouki R, Audouze K. Endocrine disrupting chemicals and COVID-19 relationships: a computational systems biology approach. medRxiv. 2020;2020. Available from: https://doi.org/10.1101/2020.07.10.20150714.
60. Fabregat A, Jupe S, Matthews L, Sidiropoulos K, Gillespie M, Garapati P. The Reactome Pathway Knowledgebase. Nucleic Acids Research. 2018;46:649–55. PMID: 29145629. Available from: https://doi.org/10.1093/nar/gkx1132.
61. Kanehisa M, Sato Y, Furumichi M, Morishima K, Tanabe M. New approach for understanding genome variations in KEGG. Nucleic Acids Research. 2019;47:590–5. PMID: 30321428. Available from: https://doi.org/10.1093/nar/gky962.
62. Slenter DN, Kutmon M, Hanspers K, Riutta A, Windsor J, Nunes N. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. Nucleic Acids Research. 2018;46:661–7. PMID: 29136241. Available from: https://doi.org/10.1093/nar/gkx1064.
63. Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. In Vivo (Athens, Greece). 2020;34(5):3023–6. PMID: 32871846. Available from: https://doi.org/10.21873/invivo.12134.
64. Pan Y, Shang Q, Fang K, Zhang J, Xi J. Down-regulated transcriptional level of Ace1 combined with mutations in Ace1 and Ace2 of Aphis gossypii are related with omethoate resistance. Chemico-Biological Interactions. 2010;188(3):553–7. PMID: 20692243. Available from: https://doi.org/10.1016/j.cbi.2010.07.022.
65. Zhuang HM, Li CW, Wu G. Identification and characterization of ace2-type acetylcholinesterase in insecticide-resistant and -susceptible parasitoid wasp Oomyzus sokolowskii (Hymenoptera: eulophidae). Molecular Biology Reports. 2014;41(11):7525–34. PMID: 25074274. Available from: https://doi.org/10.1007/s11033-014-3640-5.
66. Revuelta L, Piulachs MD, Bellés X, Castañera P, Ortego F, Díaz-Ruíz JR. RNAi of ace1 and ace2 in Blattella germanica reveals their differential contribution to acetylcholinesterase activity and sensitivity to insecticides. Insect Biochemistry and Molecular Biology. 2009;39(12):913–9. PMID: 19900550. Available from: https://doi.org/10.1016/j.ibmb.2009.11.001.
67. Dixit S, Ahsan H, Khan FH. Pesticides and plasma proteins: unexplored dimensions in neurotoxicity. International Journal of Pest Management. 2021;69(3):278–87. Available from: https://doi.org/10.1080/09670874.2021.1917725.
68. Mi H, Muruganujan A, Thomas PD. PANTHER in 2013: modeling the evolution of gene function, and other gene attributes, in the context of phylogenetic trees. Nucleic Acids Research. 2013;41(Database issue):377–86. PMID: 23193289.
69. Yao Y, Lawrence DA. Susceptibility to COVID-19 in populations with health disparities: posited involvement of mitochondrial disorder, socioeconomic stress, and pollutants. Journal of Biochemical and Molecular Toxicology. 2021;35(1):e22626. PMID: 32905655. Available from: https://doi.org/10.1002/jbt.22626.
70. Duru CE, Umar HI, Duru IA, Enenebeaku UE, Ngozi-Olehi LC, Enyoh CE. Blocking the interactions between human ACE2 and coronavirus spike glycoprotein by selected drugs: a computational perspective. Environmental Analysis, Health and Toxicology. 2021;36(2):e2021010. PMID: 34130375. Available from: https://doi.org/10.5620/eaht.2021010.
71. Baraniuk C. Receptors for SARS-CoV-2 Present in Wide Variety of Human Cells; 2020.
72. Sagawa T, Tsujikawa T, Honda A, Miyasaka N, Tanaka M, Kida T. Exposure to particulate matter upregulates ACE2 and TMPRSS2 expression in the murine lung. Environmental Research. 2021;195:110722. PMID: 33422505. Available from: https://doi.org/10.1016/j.envres.2021.110722.
73. Li HH, Liu CC, Hsu TW, Lin JH, Hsu JW, Li AF. Upregulation of ACE2 and TMPRSS2 by particulate matter and idiopathic pulmonary fibrosis: a potential role in severe COVID-19. Particle and Fibre Toxicology. 2021;18(1):11. PMID: 33706759. Available from: https://doi.org/10.1186/s12989-021-00404-3.

74. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. American Journal of Physiology Heart and Circulatory Physiology. 2020;318(5):1084–90. PMID: 32228252. Available from: https://doi.org/10.1152/ajpheart.00217.2020.
75. Gurung AB, Ali MA, Lee J, Aljowaie RM, Almutairi SM. Exploring the phytochemicals of Platycodon grandiflorus for TMPRSS2 inhibition in the search for SARS-CoV-2 entry inhibitors. Journal of King Saud University Science. 2022;34(6):102155. PMID: 35702062. Available from: https://doi.org/10.1016/j.jksus.2022.102155.
76. Shapira T, Monreal IA, Dion SP, Buchholz DW, Imbiakha B, Olmstead AD, et al. TMPRSS2 inhibitor acts as a pan-SARS-CoV-2 prophylactic and therapeutic. Nature. 2022;605(7909):340–8. PMID: 35344983. Available from: https://doi.org/10.1038/s41586-022-04661-w.
77. Mahoney M, Damalanka VC, Tartell MA, Chung DH, Lourenço AL, Pwee D. A novel class of TMPRSS2 inhibitors potently block SARS-CoV-2 and MERS-CoV viral entry and protect human epithelial lung cells. Proceedings of the National Academy of Sciences of the United States of America. 2021;118(43):e2108728118. PMID: 34635581. Available from: https://doi.org/10.1073/pnas.2108728118.
78. Gan X, Huang H, Wen J, Liu K, Yang Y, Li X. α-Terthienyl induces prostate cancer cell death through inhibiting androgen receptor expression. Biomedicine and Pharmacotherapy. 2022;152:113266. PMID: 35691152. Available from: https://doi.org/10.1016/j.biopha.2022.113266.
79. Bian H, Zheng ZH, Wei D, et al.. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. medRxiv. 2020:2020.2003.2021.20040691.; 2020. Available from: https://doi.org/10.1101/2020.03.21.20040691.
80. Pushkarsky T, Yurchenko V, Laborico A, Bukrinsky M. CD147 stimulates HIV-1 infection in a signal-independent fashion. Biochemical and Biophysical Research Communications. 2007;363(3):495–9. PMID: 17888876. Available from: https://doi.org/10.1016/j.bbrc.2007.08.192.
81. Rath S, Perikala V, Jena AB, Dandapat J. Factors regulating dynamics of angiotensin-converting enzyme-2 (ACE2), the gateway of SARS-CoV-2: epigenetic modifications and therapeutic interventions by epidrugs. Biomedicine and Pharmacotherapy. 2021;143:112095. PMID: 34479017. Available from: https://doi.org/10.1016/j.biopha.2021.112095.