Review Article

Recent Updates on Anti-Viral Drug Design Against COVID – 19 Using Suitable Enzyme Targets

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ABSTRACT

Severe acute respiratory disorder corona virus 2 (SARS-CoV-2) is a recently developing human irresistible corona virus that causes COVID -19, which has been perceived as a pandemic by the World Health Organization (WHO) on March eleventh. It is a significant wellspring of fiasco in 21st century. There is still no immunization, no complete treatment for this infection since its pathogenesis and multiplication pathways are as yet obscure. The endeavors of universal wellbeing specialists have since concentrated on Rapid determination and disengagement of patients just as the quest for treatments ready to counter the most genuine impacts of the illness. This sickness or infection presents an unpredicted test to recognize powerful medication for anticipation and treatment. In any case, the absence of explicit medications to forestall or treat an attack is a significant need at this present purpose of time. In such manner, we led an efficient audit to recognize major druggable target in coronavirus.

Keywords: Coronavirus, COVID-19, Drug Targets, Therapies, SARS.

INTRODUCTION

Human corona viruses (CoVs) are enveloped viruses with a positive - sense single stranded RNA genome. At present, six human Corona viruses have been accounted for including human coronavirus 229E (HCoV - 229E), OC43 (HCoV - NL63), HKUI (HCoV - HKUI), severe acute respiratory syndrome corona virus (SARS - CoV) and Middle East respiratory disorder corona virus (MERS - CoV). MERS-CoV and SARS-CoV and 2019 - novel corona virus (nCoV), liable for the disease with special reference to involvement of the respiratory tract (both upper and lower respiratory tract) eg. Common cold, pneumonia, bronchiolitis, rhinitis, pharyngitis, sinusitis, and other system symptoms, for example, infrequent water and diarrhea. Among these seven strains, three strains proved to be highly pathogenic (SARS - CoV, MERS - CoV, 2019 nCoV), which caused endemic of severe CoV disease.[1] The reservoir of SARS - CoV is unknown, but bats and ensuing spread to Himalayan palm civet are hypothesized.[2] MERS-CoV additionally has a zoonotic source in the middle East, and the transmission is through camel .Among these, the SARS - CoV outbreak began in 2003 in Guangdong region of China and the second outbreak of MERS-CoV episode in 2012 in Saudi Arabia.[2,3,4] Past to these attacks, CoV was known to cause milder sickness, and these two outbreak featured their versatile potential to the changing condition and they are grouped under "rising infection". Information about the structure, metabolic pathways of CoV and pathophysiology of CoV related ailment is essential to recognize conceivable medication targets. [5]

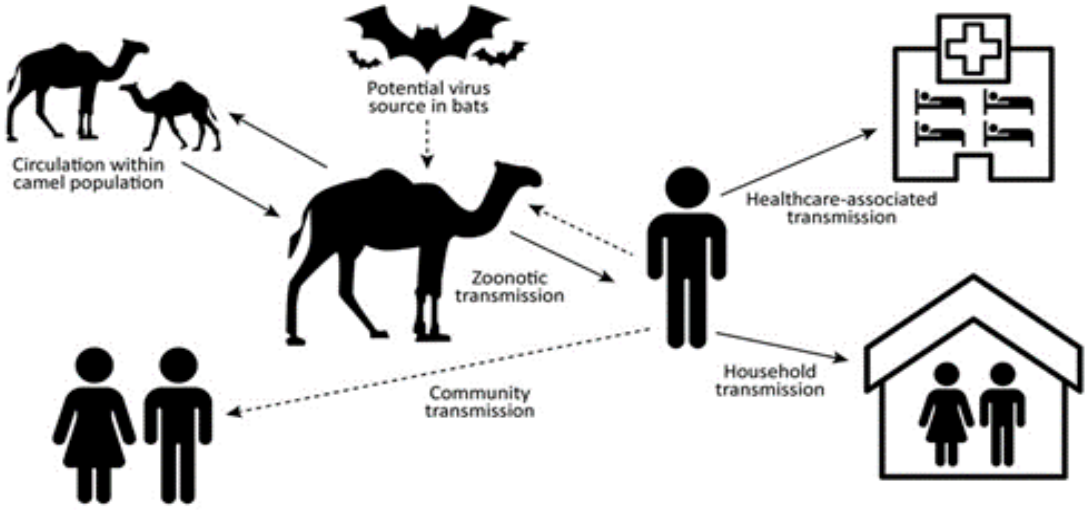

Figure 1: Middle East Respiratory Syndrome Coronavirus [47]

The most significant basic proteins of CoV are spike(S) protein, membrane(M) protein, envelope(E) protein and the nucleocapsid (N) protein. A portion of the infections, for example, beta - CoV likewise have hemagglutinin esterase (HE) glycoprotein.[6] The RNA genome of CoV has seven qualities that are monitored all together . ORF1a,ORF1b, S, OEF3, E, M, N in 5' to 3' course. The two third piece of the RNA genome is secured by the ORF1a/b,which produces the two viral replicase proteins that are polyprotein (PP1a and PP1ab).[7] 16 develop non basic proteins (NDPs) emerge from further handling of these two PPs. These NSPs partake in various viral capacities including the arrangement of the replicase transcriptase complex.The remaining genome part of the infection encodes the mRNA which creates the structural proteins i.e spike, envelope, membrane and nucleocapsid, and other accesory proteins.[7] The RNA genome of CoV is pressed in the nucleocapsid protein and further secured with envelope.[9]

Transmission of Coronavirus

If there should arise an occurrence of SARS - CoV, transmission is through droplet infection (respiratory secretion) and close person to person contact.[9,10] It can also spread through sweat, stool, urine, and respiratory secretion. At the point when infection goes into the body, it binds to the essential target cells, for example, enterocytes and pneumocytes[9,10,] in this way setting up a pattern of disease and replication. Other target cells of CoV are epithelial renal tubules, tubular epithelial cells of kidney, immune cells and cerebral neuronal cells.[9,10] Corona virus attaches to target cells with the assistance of spike protein-have cell protein interaction (ACE - 2) in SARS-CoV and dipeptidyl peptidase - 4 (DPP-4) in MERS – CoV. [11]

After the receptor acknowledgment, the infection genome with its nucleocapsid is discharged into the cytoplasm of the host cells. The viral genome contains ORF1a and ORF1b genes, which produces two PPs that are PP1a and PP1b [12], which assists with assuming responsibility for have ribosomes for their own translation process.[13] Both PP1a and PP1b take part in the development of the replication transcription complex.[12] After process ofhandling PP by protease, it produces 16 NSPs. All NSPs have a significant job in the replication and transcript particle.

Integrated proteins, for example, M, E and S are gone into the endoplasmic reticulum (ER) - Golgi transitional compartment (ERGIC) complex and make the structure of viral envelope.[14] Then again, the replicated genome binds to N protein and structures the ribonucleoprotein (RNP) complex. The external spread is framed by the M, E, and S proteins.[14] At last, the infection particles comes out of the ERGIC by making a bud like structure.[15] These develop virions structure a vesicles, which fuses with the plasma membrane and discharge the infection particles into the extracellular region.[15,16]

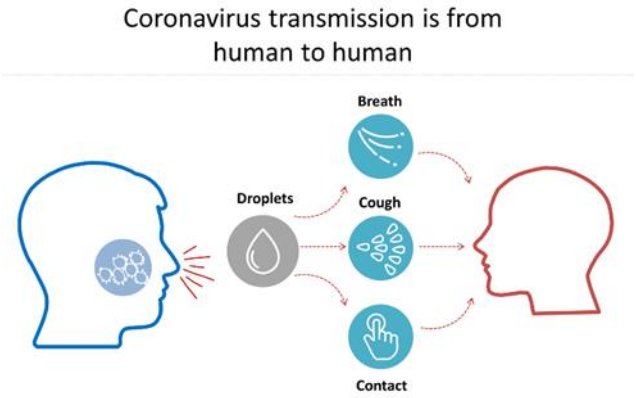

Figure 2: Human to Human Transmission

Spike Protein

The spike protein is a cleaved shape, type - TM protein.[17] The spike protein assumes a significant job in viral entry into the host.[18] Beginning interaction between the S1 area and its host receptor (ACE - 2 if there should arise an occurrence of SARS-CoV and PP4 in the event of MERS - CoV) and resulting S2 segment mediated fusion of the host and viral membrane permitted the coronavirus RNA genome to enter inside the host cells and hence, these proteins speak to as significant focuses from Drug Discovery side.[18] Spike protein additionally activate the invulnerable reaction of the host cell toward coronavirus.[18]

S1 domain - The primary part of the S1 domain are the n-terminal domain (NTD) and the c-terminal domain (CTD). The S1 domain go about as a significant antigen on the outside of infection and has a receptor binding domain (RBD).[19] The 18 residues of ACE - 2 interface with the RBD(contains 14 aminoacids) of SARS-CoV spike protein[20] and for this contact,K341 of ACE - 2 and R453 residues of RBD assume the most significant job. On the off chance that point transformed on the D454 or R441 of RBD, it disturbs the coupling activity. The S1 domain associating with the ACE - 2 or DPP - 4 receptors of the host against - ACE - 2 immune response blocked viral section replication in Vero E6 cells. [20,21]

S2 domain - The S2 subunit has 2 heptad regions (HR1 and HR2) and hydrophobic fusion peptide. [19] Medication planning techniques focusing on S protein and its interactions. The RBD is focused in many medication planning considers peptide succession with grouping also to the RBD of S protein hampered S1 - RBD: ACE - 2 association and prevented entry of SARS - CoV into Vero cells. [19,22,23]

A SARS - CoV RBD explicit immunizer (FM6) neglected to restrain the event of disease.

Chloroquine, an anti malarial agent inhibits SARS -CoV by elevation of endosomal pH and changes the terminal glycosylation of ACE - 2, which ultimately obstruction with the virus receptor binding.[24]

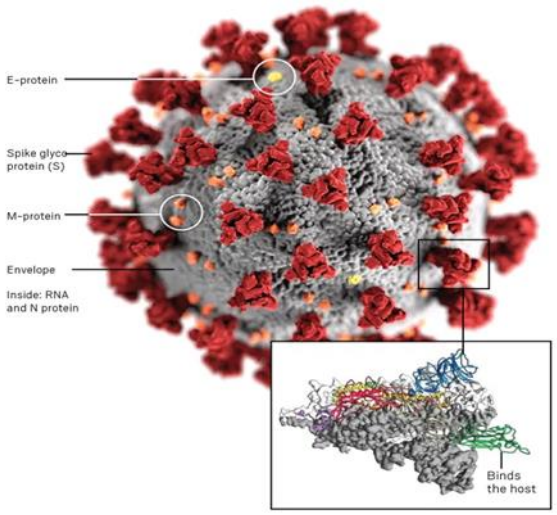

Figure 3: Coronavirus Target Proteins

Envelope Protein (E)

The E protein is the smallest TM basic protein of corona virus. Two particular domains contain the E protein, the hydrophobic domain and the charged cytoplasmic tail. In any case, the structure is profoundly factor among various individuals from the coronavirus family. [25] E Protein has an exceptional job in viral morphogenesis, uncommonly during gathering and egress. [25] CoV lacking E protein show lower viral titer, immature and wasteful progenies.[26,27] Oligomerization of a protein prompts to the arrangement of Ion channel.[28] Be that as it may, significance of these Ion channels is as yet not satisfactory. E protein likewise go about as a destructiveness factor.[25] Protein has a significant job in corona virus get together and sprouting arrangements.[16] Aside from this, E protein found around the ER and Golgi body locales.[27] Hexamethyleneamiloride obstruct this protein related ion channel action in the mammalian cell communicating SARS - CoV envelope protein.[29]

Upkeep of the shape of viral envelope is the most significant capacity of the M protein[35] and the M protein play out this activity by communicating with other CoV proteins[30], consolidation of Golgi Complex into new virions [27] and adjustment of nucleocapsid protein.[27]

The M protein is characterized by 3 TM domain[31] with c-terminal inside and n-terminal outside.[30] Through different protein-protein communications, the M protein assumes an essential job in viral intracellular homeostasis.[27]

Collaboration between M-M, M-S, M-N protein takes an uncommon part in viral assembly.[27] The M-S interaction are fundamental for the connection of spike protein in the ERGIC complex, which is later consolidated into new popular Progenies.[27] The M-N association are critical for the adjustment of RNP Complex, which frames the viral Core.[27] The M protein and N protein are the major viral envelope proteins, characterizing viral shape, however it likewise takes part in the development and arrival of infection like particles.[27] M protein additionally participates in the adjustment of the Envelope protein.

Nucleocapsid Protein (N)

The structure of nucleocapsid protein is moderated across various individuals from the corona virus family. The three qualities intrinsically disordered regions (IDRs) of the nucleocapsid protein are N - arm, Central linker(CL) and C – tail. [4] The NTD and CTD are the major auxiliary and useful domain of nucleocapsid protein. The most significant capacity of the N protein NTD is RNA binding, while the essential employment of the CTD is a demerization.[4,5] As the CL district is wealthy in arginine and serine buildup of substance, it likewise contains countless phosphorylation sites.[32] The C-terminal IDRs take a significant part in nucleocapsid protein oligomerization and N-M protein interaction.[33]

Development and support of the RNP complex are the most significant capacity of the N protein.[7] It likewise control the replication and interpretation of viral RNA and in the host, it restrains protein interpretation through EF 1 alpha mediated activity [7], modification of host cell digestion, have cell cycle and adoptosis.[6,7] In human fringe blood, and N protein restrain cell expansion through the hindrance of cytokinesis.[2,5]

The NTD contains destinations for RNA official. The RNA restricting locales on the N protein were recognized by watching its interaction with ribonucleoside 5'-monophosphate (AMP, UMP, CMP, and GMP).[32] Using the data about connection among AMP and UMP binding to the NTD of nucleocapsid protein, inhibitors of RNA restricting were structured. Binding of PJ34 on NTD influences the genome official and replication procedure of Corona infection.[32]

The CTD of N protein has an essential job in oligomerization, particularly the C-terminal end. A C-terminal tail peptide arrangement N377-389 contends with the oligomerization procedure and critical hindrance of viral titer was seen at 300 micrometer focus .N220, which is a nucleocapsid protein peptide,demonstrated a high restricting partiality to people MHC-1 in T2 cells and the peptide grouping was effective in activating T-cell.

Proteases

The SARS - CoV genome encodes various protein. The replicase gene, which is a significant segment of CoV genome encoded for 16 NSPs as two huge PPs (PPa and PPab).[33] Two types of cysteine protease follow up on the PPs to discharge the NSPs. The C-terminal end of these PPs is cut by chymotrypsin like cysteine protease (fundamental protein (Mpro or 3C-like protease (3CLpro))and the N-terminal end is handled by the M Mpro (otherwise called papin like protease (PLpro).[34] The initial three cleavage of PPS is cut by PLPro while the rest 11 sites are cut by CLpro, and this cleavage bring about arrival of 16 NSPs.

3C-LIKE PROTEASE: The CL Pro is available in homodimer structure and has cys-his dyad a functioning site which shows protease movement. Whenever transformed on the Ser139 and phel140 position, it abrogates the dimerization

of the 3CLpro.[35] The protease can cut 11 locales in P1 position of pp1a and pp1ab and can create a develop protein that stays the replication/translation complex.[6]

Papain - Like Protease

The PLpro cleaves the N - Terminal locale of the PP to create three NSPs i.e NSP1,2,3.[6,34] PLpro has a catalytic center domain that contain 316 amino acids, which is liable for separating replicase substrates, and an agreement succession LXGG was required for cleavage.[36] Higher dosages of zinc and Zinc conjugates were found to hinder the two types of SARS protease (CLpro and PLpro). A large number of the protease inhibitors are being utilized in the treatment of covid-19 mode: lopinavir-ritonavir combination.[37]

Hemagglutin Esterase

The Hemagglutin esterase protein is available in the envelope of CoV, all the more exceptionally among beta-coronaviridiae.[38] The Hemagglutin esterase intervenes reversible attachement to O-acetylated-sialic-acids by acting both as lectin and as receptor crushing compounds.[38]

NTPase/Helicase

NTPase/Helicase assumes the significant job in central dogma of the infection.[39] SARS-CoV helicase compound is an individual from the SF1. This protein inclines toward ATP, dATP and dCTP as a substrate, it likewise hydrolyzed all NTPs.[40] Poisonousness issues are primary hindrances in the advancement of inhibitors of helicase, and nonspecificity of inhibitors may cause genuine harmfulness.[39] Notwithstanding, in spite of hypothetical impediments, helicase is by and large progressively perceived as a druggable objective for various disease conditions.[41]

Different Methodologies to Counter Corona Infection: Endosomal PH

Once went into the host cell, the ensuing life pattern of SARS -CoV required low pH.[42] Inhibitors of pH delicate endosomal protease square CoV disease.[42,43] A few distinctive small compounds and atoms have been accounted for against infection contamination. Amiodarone gets collected in the acidic organelles. vacuoles on presentation to amiodarone shows modification in intracellular organelles especially enlargement of late endosomes. *In vitro* condition, amiodarone restrained coronavirus contamination in Vero cells.[44] At priori trypsin, cleavage of S protein is fundamental for a fruitful viral section. In any case, trypsin cleavage likewise doesn't influence the viability of amiodarone.[44]

Clinical Updation of 2019 on Coronavirus

In response to the CoV disease 2019 (COVID-19) emergency, clinical trial research assessing the efficacy and safety of clinical candidate intervention to treat COVID-19 are emerging at an unprecedented rate.[45] As of April 21,2020, well more than 500 clinical trials have been enlisted at the different worldwide and national clinical trial registry sites. Finding from randomised clinical trials that have been published as of April 21,2020, have investigated the efficacy of lopinavir-ritonavir compared with standard of care, Hydroxychloroquine compared with best supportive care, Favipiravir compared with arbidol, and lopinavir-ritonavir compared with arbidol.

Other non randomised trials have investigated Hydroxychloroquine versus Hydroxychloroquine combined with azithromycin.

Over 300 trials are enrolling participants and cover further investigations of the above drugs and promising therapies such as remdesivir, 1L-6 inhibitors (tocilizumab and sarilumab), convalescent plasma therapy, stem cell transfusion, vaccine candidates, several other well known direct acting anti- viral, and traditional Chinese medicine.[45] Most of these trials will offer comparative efficacy data versus standard of care according to local COVID-19 treatment guidelines, but a handful of randomised control trials will provide head to head evidence between high profile interventions.[45]

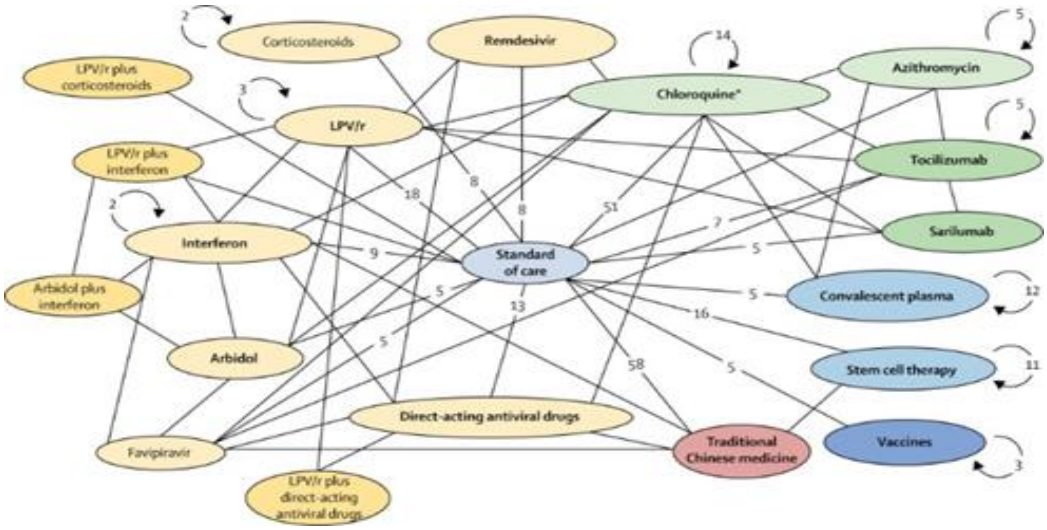

Figure 4: Clinical Trials[45]

Coronavirus Vaccines

More than 90 antibodies are being created against SARS-CoV-2 by explore groups in organizations and colleges over the world.[46] Analysts are trialing various innovations, some of which haven't been utilized in a licensed vaccine before. At least six groups have just started infusing formulations into volunteers in safety trials; others have begun testing in animals.[46]

An array of vaccines

All vaccines aim to expose the body to an antigen that won't cause disease, but will provoke an immune response that can block or kill the virus if a person becomes infected.[46] There are at least eight types being attempted against the coronavirus, and they depend on various infections or viral parts.[46]

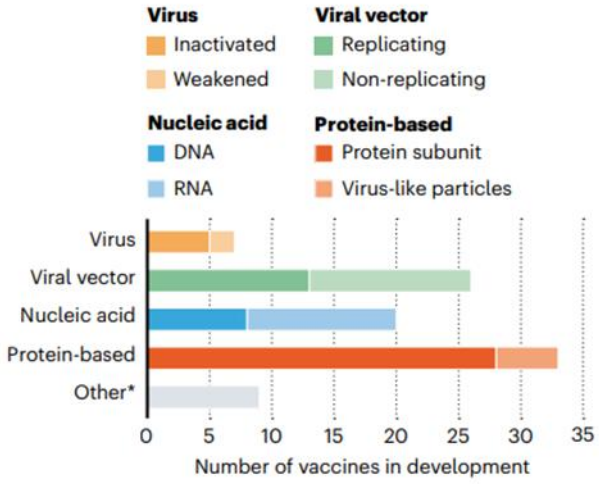

Figure 5: Array of Vaccines[46]

CONCLUSION

Drug Discovery against the Corona infection is a difficult activity attributable to visit recombination occasions. The advancement of an antibody is another significant perspective. Human corona virus (HCoV) uses host cell segments to accomplish the different physiological procedures, including viral passage, genomic replication, and the get together and sprouting of virions, in this manner bringing about neurotic harm to the host. We need progressively auxiliary science details and details of the existence pattern of the corona virus, which can accelerate the medication/immunization advancement process against corona virus. Once more, as a preventive measure, severe carefulness of viral changes in various hosts for expectation of an occasion is significant.

REFERENCES

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections-More than just the common cold. JAMA, 323, 2020, 707. DOI: 10.1001/jama.2020.0757,PMID:31971553.
2. Saif LJ. Animal coronaviruses: What can they teach us about the severe acute respiratory syndrome? Rev Sci Tech., 23, 2004,643–60. DOI:10.20506/rst.23.2.1513,PMID:15702725.
3. Yang H, Bartlam M, Rao Z. Drug design targeting the main protease, the Achilles' heel of coronaviruses. Curr Pharm Des.,12,2006,4573–90.DOI;10.2174/138161206779010369, PMID;17168763.
4. Chang CK, Lo SC, Wang YS, Hou MH. Recent insights into the development of therapeutics against coronavirus diseases by targeting N protein. Drug Discov Today,21,2016,562–72. DOI:10.1016/j.drudis.2015.1.015,PMID:26691874.
5. Alsaadi JE, Jones IM. Membrane binding proteins of coronaviruses. Future Virology, 14, 2019, 275–86. DOI:10.2217/fvl-2018-0144, PMID:3201500.
6. Hilgenfeld R. From SARS to MERS: Crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS J.,281,2014,4085–96. DOI:10.1111/febs.12936,PMID:25039866.
7. McBride R, van Zyl M, Fielding BC. The coronavirus nucleo capsid is a multifunctional protein. Viruses, 6, 2014, 2991–3018. DOI:10.3390/v6082991, PMID:25105276.
8. Devaux A.Christian, Rolan Marc – Jean, Coson Philippe,Raoult Didier, New insights on the anti-viral effect Chloroquine against coronavirus : what to expect for COVID Int.J.Microb Agent, 55, 2020, 105938. DOI:10.1016/j.ijantimicag.2020.105938,PMID:32171740.
9. Guo Y, Korteweg C, McNutt MA, Gu J. Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res.,133,2008,4–12.DOI:10.1016/j.virusres.2007.01.22, PMID:17825937.
10. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol., 170, 2007, 1136–47.DOI:10.2353/ajpath.2007.061088,PMID:17392154.
11. Mubarak A, Alturaiki W, Hemida MG. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Infection, Immunological Response, and Vaccine Development. J Immunol Res. 2 019, 1–11. DOI:http://doi.org/10.1155/2019/6491738,PMID:64917378.
12. Dte Velthuis AJ, van den Worm SH, Snijder EJ. The SARS-coronavirus nsp7+nsp8 complex is a unique multimeric RNA polymerase capable of both *de novo* initiation and primer extension. Nucleic Acids Res.,40,2012,1737–47. DOI:10.1093/nar/gkr893, PMID:22039154.
13. Stobart CC, Sexton NR, Munjal H, Lu X, Molland KL, Tomar S, et al. Chimeric exchange of coronavirus nsp5 proteases (3CLpro) identifies common and divergent regulatory determinants of protease activity. J Virol.,87,2013,12611–8.DOI:10.1128/JVI.02050-13, PMID:24027335.
14. Narayanan K, Maeda A, Maeda J, Makino S. Characterization of the coronavirus M protein and nucleocapsid interaction in infected cells. J Virol., 74, 2000, 8127–34. DOI:10.1128/jvi.74.17.8127-8134.2000, PMID:10933723.
15. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol., 14, 2016, 523–34. DOI:10.1038/nrmicro.2016.81,PMID:27344959.
16. Nieto-Torres JL, Dediego ML, Alvarez E, Jiménez-Guardeño JM, Regla-Nava JA, Llorente M, et al. Subcellular location and topology of severe acute respiratory syndrome coronavirus envelope protein. Virology, 415,2011,69–82.DOI:10.1016/j.viron.2011.03.029, PMID:21524776.
17. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses, 4,2012,1011–33.DOI;10.3390/V4061011, PMID;22816037.
18. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol., 3, 2016, 237–261. DOI: 10.1146/amnurev-virology-110615-042301, PMID:27578535.
19. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol., 7, 2009, 226–36. DOI:10.1038/nrmicro2090,PMID:19198616.
20. Prabakaran P, Xiao X, Dimitrov DS. A model of the ACE2 structure and function as a SARS-CoV receptor. Biochem Biophys Res Commun.,

314, 2004, 235–41. DOI:10.1016/j.bbrc.2003.12.081,PMID:14715271.

21. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature, 426, 2003, 450–4. DOI:10.1038/nature02145,PMID:14647384.

22. Hu H, Li L, Kao RY, Kou B, Wang Z, Zhang L, et al. Screening and identification of linear B-cell epitopes and entry-blocking peptide of severe acute respiratory syndrome (SARS)-associated coronavirus using synthetic overlapping peptide library. J Comb Chem.,7(5),2005,648–56. DOI:10.1021/cc0500607,PMID:16153058.

23. Han DP, Penn-Nicholson A, Cho MW. Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology, 350,2006, 15–25. DOI:10.1016jvirol.2006.01.029,PMID:16510163.

24. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J.,2,2005,69. DOI:10.1186/1743-422x-2-69,PMID:16115318.

25. Venkatagopalan P, Daskalova SM, Lopez LA, Dolezal KA, Hogue BG. Coronavirus envelope (E) protein remains at the site of assembly, Virology, 478, 2015, 75–85. DOI:10.1016/j.virol.2015.02.005,PMID:25726972.

26. Kuo L, Hurst KR, Masters PS. Exceptional flexibility in the sequence requirements for coronavirus small envelope protein function. J Virol., 81, 2007, 2249–62. DOI:10.1128/JVI.01577-063, PMID:17182690.

27. Schoeman D, Fielding BC. Coronavirus envelope protein. Virology,16(1),2019,69.DOI:10.1186/s12985-019-1182-0,PMID:31133031.

28. Arbely E, Khattari Z, Brotons G, Akkawi M, Salditt T, Arkin IT. A highly unusual palindromic transmembrane helical hairpin formed by SARS coronavirus E protein. J Mol Biol.,341(3),2004,769–79. DOI:10.1016/j.jmb.2004.06.044,PMID:15288785.

29. Pervushin K, Tan E, Parthasarathy K, Lin X, Jiang FL, Yu D, et al. Structure and inhibition of the SARS coronavirus envelope protein ion channel, PLoS Pathog., 5(7),2009, e1000511. DOI:10.1371/journal.ppat.1000511,PMID:19593379.

30. Hogue BG, Machamer CE. Coronavirus structural proteins and virus assembly. Nidoviruses,ResearchGate,2008,179–200.DOI: 10.1128/9781555815790.ch12.

31. Arndt AL, Larson BJ, Hogue BG. A conserved domain in the coronavirus membrane protein tail is important for virus assembly. J Virol., 84(21), 2010, 11418–28. DOI:10.1128/JVI.01131.10,PMID:20719948.

32. Lin SY, Liu CL, Chang YM, Zhao J, Perlman S, Hou MH. Structural basis for the identification of the N-terminal domain of coronavirus nucleocapsid protein as an antiviral target. J Med Chem., 57(6), 2014, 2247–57. DOI:10.1021/jm500089r,PMID:24564608.

33. Chang CK, Hou MH, Chang CF, Hsiao CD, Huang TH. The SARS coronavirus nucleocapsid protein – Forms and functions. Antiviral Res., 103, 2014, 39–50. DOI:10.1016/j.antiviral.2013.12.009,PMID:24418573.

34. Lindner HA, Fotouhi-Ardakani N, Lytvyn V, Lachance P, Sulea T, Ménard R. The papain-like protease from the severe acute respiratory syndrome coronavirus is a deubiquitinating enzyme. J Virol, 79(24), 2005, 15199–208. DOI:10.1128/JVI.79.24.15199-15208.2005, PMID:16306591.

35. Hu T, Zhang Y, Li L, Wang K, Chen S, Chen J, et al. Two adjacent mutations on the dimer interface of SARS coronavirus 3C-like protease cause different conformational changes in crystal structure. Virology,388(2),2009,324–34. DOI:10.1016/j.virol.2009.03.034,PMID:19409595.

36. Barretto N, Jukneliene D, Ratia K, Chen Z, Mesecar AD, Baker SC. The papain-like protease of severe acute respiratory syndrome coronavirus has deubiquitinating activity. J Virol,79(24),2005,15189–98.DOI:10.1128/JVI.79.24.15189-15198.2005,PMID:16306590.

37. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR, J Korean Med Sci., 35(6) 2020, e79.DOI:10.3346/jkms.2020.35.e79, PMID:32056407.

38. Zeng Q, Langereis MA, van Vliet AL, Huizinga EG, de Groot RJ. Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution. Proc Natl Acad Sci USA, 105(26), 2008, 9065–9. DOI:10.1073/pnas.0800502105, PMID:18550812.

39. Frick DN, Lam A M. Understanding helicases as a means of virus control. Curr Pharm Des, 12(11), 2006, 1315–38. DOI:10.2174/138161206776361147,PMID: 16611118.

40. Karpe YA, Lole KS. NTPase and 5' to 3' RNA duplex-unwinding activities of the hepatitis E virus helicase domain. J Virol, 84(7), 2010, 3595–602. DOI:10.1128/JVI.02130-09, PMID:20071563.

41. Banerjee T, Aggarwal M, Sommers JA, Brosh RM., Biochemical and cell biological assays to identify and characterize DNA helicase inhibitors,108,2016,130–4. DOI:10.1016/j.ymeth.2016.04.007,PMID:27064001.

42. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A,102(33),2005,11876–81. DOI:10.1073/pnas.0505577102,PMID:16081529.

43. Bertram S, Glowacka I, Müller MA, Lavender H, Gnirss K, Nehlmeier I, et al. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. J Virol, 85(24), 2011, 13363–72.DOI: 10.1128/JVI.053.00-11., PMID:21994442.

44. Stadler K, Ha HR, Ciminale V, Spirli C, Saletti G, Schiavon M, et al. Amiodarone alters late endosomes and inhibits SARS coronavirus infection at a post-endosomal level. Am J Respir Cell Mol Biol.,39(2),2008,142–149.DOI:10.1165/rcmb.2007-0217OC,PMID:18314540.

45. Thorlund Kristian, Dron Louis,Park Jay, A real time dashboard of clinical trials for covid-19, The lancet digital health, 2, 2020, 286-287. DOI: 10.1016/S2589-7500(20)30086-8, PMID:32363333.

46. Callaway Ewen, The race of coronavirus vaccines: a graphical guide, Nature research, Drug Discov, 580,2020,576-577.DOI: 10.1038/d41586-020-01221-y, PMID:32346146.

47. Killerby E.M, Biggs M.Holly, Midgley M.C, Watson T.John, Middle East Respiratory Syndrome Coronavirus Transmission, Emerging Infectious disease, 26, 2020, 191-198. DOI: 10.3201/2eid2602.190697,PMID:31961300.

48. Pillaiyar Thanigaimalai, Meenakshisundram Sangeetha, Manickam Manoj, Recent discovery and development of inhibitors targeting coronavirus.Drug discov today,4,2020,668 -688.

DOI: 10.1016/j.drudis.2020.01.015,PMID: 32006468.

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