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# UNDERSTANDING SARS AND MERS FOR TARGET-SPECIFIC DRUG DISCOVERY AGAINST SARS-CoV-2: A REVIEW

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**Abstract**
The pandemic COVID-19 caused by the newly discovered SARS-CoV-2 is a challenge to our society and scientists. Keeping severity of pandemic at front, pace for vaccine development has increased drastically; almost 10 vaccines are in phase-III. It requires fast scientific discovery and data generation to compete with the speed of viral spread. This paper is accumulation of small efforts and scattered knowledge of SARS-CoV-2 virology and other pandemics due to coronavirus.

No drug has been approved so far for COVID-19 and only a few for SARS and MERS. The ongoing trails are testing random drugs from databases due to urgency. This global public health crisis of the present generation requires high volume of clinical trials for potential therapies for COVID-19 investigation.

Searching for synthetic drugs as well as natural products like plant metabolites which could be beneficial for this purpose will widen our knowledge. Pathways study of secondary metabolite synthesis, plant physiology and phytochemistry are important for drug development.

This report includes various synthetic and natural drugs which might show potential activity against Coronavirus and is focused on the mechanism of infection by COVID-19 and different inhibition sites available to check viral entry inside the host cell. Inhibiting the sites for jamming viral replication inside the host cell after the infection is another way of fighting infection spread in body. Exploring different sites of inhibition will increase the possibility of obtaining drug for Coronavirus. Natural products proved more useful than synthetic drugs because of its effectiveness and less side effects. Therefore, it is necessary to search for newly available data along with the old analyzed information and incorporating them together to obtain fruitful result.

**Keywords**
COVID-19, Synthetic drugs, SARS-CoV-2, Coronavirus, ACE2 receptor, Main protease.

## 1. Introduction

**1.1 Origin**Coronavirus is group of different types of RNA viruses which cause disease in birds and mammalian species. They cause moderate to severe infections in respiratory tract (Shereen et al., 2020). These infections also cause gastrointestinal and other central nervous system disorders (Harapan et al., 2020).

**1.2 Impact on health**
In December 2019 outbreak of unknown coronavirus started in Wuhan, China. More than 218 countries have been affected till May, 2020 by novel deadly virus, leading to more than 5 million confirmed cases and around 1.3 million deaths (Holshue et al., 2020). Symptoms include dry cough, fever and aches throughout the body similar to Pneumonia (Guan et al., 2020). It includes nasal congestion, diarrhoea and breathing difficulty in extreme cases (Zheng, 2020).

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### 1.3 Classification of virus

Coronavirus is common name used for Coronavirinae family which is further divided into two subfamily, named as Coronaviridae and Orthocoronavirinae. Coronaviridae family is classified into four genera, Alphacoronavirus, Betacoronavirus, Gamma-coronavirus and Deltacoronavirus. Alpha Coronavirus and beta coronavirus are the first twodescend from the bat gene pool. Newly discovered SARS CoV-2 belongs to Coronaviridae subfamily, betacoronavirus (Zheng, 2020). SARS CoV-2 shows genetic similarity with bat Coronavirus which suggests that it may have been emerged from bat borne virus (Khan et al., 2020).

The International Committee on Taxonomy of Viruses named this novel virus as SARS-CoV-2 on 11th February, 2020 as virus is genetically related to SARS outbreak in 2002. World Health Organization (WHO) named it COVID-19 unofficially, full form "**C**orona **V**irus **D**isease of 20**19"**.

### 1.4 Structure of coronavirus

SARS-CoV-2 has complex structure. It contains positive sense single stranded RNA (+ss RNA). It is very similar to SARS and related to other coronaviruses. It ranges from 50-200 nanometre diameter with 26-32 kb genome size (Lin et al., 2020). It contains four structural proteins, (S) Spike protein, (N) nucleocapsid, (E) envelope and (M) membrane proteins for specific functions. They are functional during different stages of infection (Astuti et al., 2020).

## 2 Epidemiology

### 2.1 SARS CoV:

Emerged in Guangdong province of China and rapidly escalated all over the world. It occurred in November 2002 and contains similar to Pneumonia with high risk of transmission (Báez-Santos et al., 2015). Faster transmission led to second outbreak in short span of time in HongKong. According to the reports 8100 people were infected by SARS CoV and caused 774 deaths in total, by the end it affected 29 countries.

### 2.2 MERS CoV:

After SARS CoV attack in 2002, during June 2012 patients suddenly showed symptoms of severe Pneumonia. This was not similar to the earlier outbreak. It was emerged in Jeddah, Saudi Arabia. After analysing cluster of hospital originated cases in Jordan, it was confirmed as a new strain, MERS CoV (Khan et al., 2020). This outbreak did not stop, rather continued to spread outside of Middle East region. By 2020 updates, 2468 cases were registered and caused 851 deaths.

### 2.3 SARS CoV-2:

Firstly, few cases observed in December 2019 were like SARS (Li, 2020). Survey results showed the atypical Pneumonia was coronavirus SARS CoV-2 which also marked the return of coronavirus (Gralinski et al., 2020). They linked the virus origin to wholesale seafood market of Wuhan city (Shereen et al., 2020).It showed zoonotic transmission (Li et al., 2020). Till now, as no therapeutics is available for SARS CoV-2, the only way out of COVID-19 is lockdown and social distancing(Phan et al., 2020). It helps to control massive outbreak as transportation and public places are closed (Bai et al., 2020).

## 3. Diagnostics

Diagnostics of viral diseases require trained staff at every step. BSL-2 level laboratory conditions are required for testing COVID-19 and maintaining these conditions is not easy. Following standard operating procedures is a necessity as directed by WHO (Mourya et al., 2020).

All coronaviruses diseases are detected using similar type of kit testing methods available from different countries. These kits are based on Reverse-trascriptase PCR (Wu et al., 2020). It contains primers and probes specific for disease (Khan et al., 2020). They are usually designed for targeting various sites in the genome of virus. The virus is mutating fast, many mutants have been reported so far (Sarkar et al., 2020). Research is going on for development of serological tests. It will help in understanding disease and cross reactivity better. Collecting sera for future uses is important and recommended. Newly developed is also in race for SARS CoV-2 diagnosis technologies like Clustered Regularly Interspaced Short Palindromic Repeats.

## 4. Comparison between SARS CoV, MERS and SARS CoV-2

There are four subfamilies of coronaviruses, in which betacoronavirus and alphacoronavirus infects humans while gammacoronavirus and deltacoronavirus cause disease in aves mostly. SARS CoV, SARS CoV-2 and MERS CoV belong to betacoronavirus subfamily.

SARS CoV-2, MERS CoV and SARS CoV-2 are believed to be originated by bats. Some variation from original strain is found in ORF3b, clade2 of S region and ORF8 sequence (Guan Y, 2003). These ORF encodes proteins for binding, fusion and replication (Bauch et al, 2020).

As adaptation of SARS CoV-2 is not confirmed but it shows homology with Bat-derived SARS Coronaviruses which are namely bat-SL-CoVZC45 and bat-SL-CoVZXC21. Result shows approximately 88% identity with these strains (Khan et al., 2020). Even though variations are present at residues, i.e. 8a protein absent and changes in amino acid numbers in 8a or 3c proteins in new COVID-19, the receptor binding domain is somehow similar (Belouzard et al., 2009).On contrary, primary protease is conserved in SARS CoV and SARS CoV-2 and it shares 96% similarity.

**5. Mutations and evolution of SARS-CoV-2**

Genetic diversity in the SARS-CoV-2 genome arises from randomly occurring mutations subject to selection and recombination events during replication, leading to alterations in the amino acid composition of viral proteins. Significantly, the Spike protein of SARS-CoV-2 shows varying mutation counts within its Receptor-binding Domain (RBD) across different clades. Some strains have 1-3 mutations, while the latest Omicron variant stands out with an exceptionally high count, featuring up to 37 mutations in the spike protein, including 15 in the RBD. Notably, around 25 of these mutations were unique to the Omicron variant.

The JN.1 variant, detected in September 2023, is associated to BA.2.86 (commonly known as "Pirola"), a branch of the Omicron variant. As of late December, JN.1 constituted 44% of cases, as reported by the Centers for Disease Control and Prevention. On December 18, the World Health Organization designated it as the latest "variant of interest" due to genetic advantages and increasing global prevalence. JN.1 has a spike protein mutation, potentially offering additional immune evasion, as per initial studies. The original Omicron strain is no longer circulating.

Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressureThe JN.1 subvariant demonstrated significantly greater immune escape capabilities than BA.2.86. In addition, JN.1 showed a stronger resistance to plasma neutralization compared to other competing variants. The Omicron subvariant BA.2.86 contains more than 30 amino acid mutations in the Spike protein relative to BA.2 and XBB.1.5. Studies indicate that neutralizing antibody responses against BA.2.86 were reduced by 5- to 13-fold compared to BA.2.

The dominating variant Omicron exhibits a substantial number of mutations, including K417, S477N, T478K, E484A and N501Y, which are shared with few other previously identified variants. Mutated RBD in Omicron serves better affinity for ACE2 and Spike protein binding, hence leading high transmissibility than others. Moreover, this bonding is stabilized by replaced uncharged residues by positively charged (Arg and Lys). This enhanced viral evasion as for now poses high risk of reinfection and for now its sub lineages are most circulating variants surpassing other variants.

**6. Variants of Coronavirus**

After May 2022, the CDC only listed one as a Variant of Concern (VOC) and that is the Omicron variant which further dropped in March 3, 2023 when ECDC de-escalated all variants from VOC and

**6.1 Tagets-** Targeting the GRP78-Dependant SARS-CoV-2 Cell Entry by Peptides and Small

**GRP78-**

GRP78 has been recognized as an attachment factor for the Middle East respiratory syndrome coronavirus (MERS-CoV), which improves the entry of the virus in the presence of DPP4, and as one of the SARS-CoV entry receptors in the human cell.The Omicron RBD shows reduced average binding affinity to GRP78 (-9.68 ± 0.63 kcal/mol) compared to the WT RBD (-8.83 ± 0.60 kcal/mol). This indicates a higher likelihood of association between the Omicron spike and the host-cell surface receptor GRP78 than the WT spike.csGRP78 functions as a receptor facilitating ACE2-independent entry of the SARS-CoV-2 spike protein into monocytes.

**7. After effects of mutations in virus**

SARS-CoV-2 evolved at a steady rate, acquiring about two mutations per month globally from December 2019 to October 2020. We've learned about the functional impact of spike protein mutations through investigations focused on changes that rapidly become prevalentor are associated with unusual epidemiological trends. Following the emergence of the D614G mutation in the receptor-binding motif (RBM), the N439K mutation appeared in Scotland in March 2020. While the initial lineage with N439K (B.1.141) disappeared, another lineage (B.1.258) independently acquired N439K and spread across Europe. N439K enhances the virus's binding to ACE2 and reduces neutralization by certain antibodies in recovered individuals. The Y453F mutation in the spike protein's RBM, known for its increased ACE2 binding, gained attention, especially in a Danish lineage initially called 'cluster 5' (now B.1.1.298). By November 5, 2020, all 214 people infected with mink-related SARS-CoV-2 carried Y453F. The B.1.1.298 lineage also had a Δ69–70 mutation in the amino-terminal domain (NTD), found in various SARS-CoV-2 populations, including the second N439K lineage (B.1.258). This Δ69–70 mutation alters an exposed NTD loop and may increase infectivity.

**8. Drug discovery**

Molecular modelling can be used to study complex chemical and biological properties. When computational and experimental methods are integrated, novel compounds are identified. Under current situation, scientists need to inovate the novel drugs for the deadly virus. As coronavirus infection is already a pandemic, therefore to come up with better and innovative therapeutics is the need of the hour.

**8.1 Mechanism of infection**

To explore treatments, it is necessary to understand whole mechanism of attack and infection of Coronavirus. This is the earliest and crucial step of viral infections in any type of host cells which determines cross species infection possibility. Study of receptor and enzymes unfolds its mechanism of infection and helps find the target for drugs. This is

the first target in designing the appropriate drug (Fig. 1).

Innate immune system is key controller of replication and infection of virus, interferons help in generating immune response after the viral infection. Antiviral effect could be obtained by blocking the signal pathways of host cell essential for viral entry and replication. Through further study it is known that virus uses surface protein of receptors of cells for entrance. In SARS-CoV and SARS-CoV-2 it binds to Angiotensin converting enzyme-2 (ACE-2) whereas in MERS binds to the DPP4 receptor.

Other targets could be coronavirus itself-

I. Inhibition of viral replication by blocking important enzymes of coronavirus
II. Jamming viral and membrane protein binding in human cells.
III. Prevent virus self-assembly by acting on structural proteins and degradation.

### 8.2 Different strategies available for drug development

This pandemic has forced scientists to develop new strategies for novel drug development. To develop a drug which is synthesized in laboratory is not in sight because $R_0$ value is increasing every time. $R_0$ value simply indicates number of healthy people can be infected from one active case of disease (Wu et al., 2020).This leaves us with remaining 3 strategies.

### 8.3 Drug repurposing

This is time for repurposing of existing medicines. As we know that preparation of a drug takes very long time and therefore we cannot wait for finding of drug, appropriate dosages, test on animal models and clinical trials. For example, Hydrochloroquine was repurposed for COVID-19 disease which is known drug for Malaria. Natural Interferon β-1b is a drug for treatment of Pneumonia. For repurposing of Natural Interferon β-1b including chloroquine, hydrochloroquine, ritonavir, lopanivir, and anti-inflammatory drugs, are being used for treatment of Coronavirus. The only disadvantage of repurposing of drugs against COVID-19 is their broad spectrum, they do not target only Coronavirus.

Novel actions could be verified for the available drugs through data analysis. With new adaptations in high throughput screening we can analyze ten thousand possible targets in a day (Szymański et al., 2012). Example- drugs for HIV infection- lopinavir/ ritonavir, a combination of protease inhibitor recently used for SARS CoV-2 patients (Dierynck et al., 2011). Though in a recent trial it was not effective in decreasing death rate and requires future analysis on patients with specific stage of infection (Cao et al., 2020).

### 8.4 Challenges in Drug Repurposing-

Differences in cultural practices, medical systems, and regulatory frameworks across countries pose challenges in fully utilizing traditional medicines and herbal medicines (TM/HMs) for COVID-19 treatment. However, some initiatives remain worthwhile.

One of the main hurdles in developing plant-based pharmaceuticals with therapeutic claims is ensuring proper quality control, accurate identification, and consistent standardization of the bioactive compounds involved.

Due to the virus's rapid mutation and the activation of additional entry pathways—such as FURIN, GRP78, CD147, NRP1, and AXL—drugs designed to target a single protein may be less effective. Consequently, natural products that can act on multiple targets offer a potential advantage over synthetic, single-target drugs.

### 8.5 Developing drug from the initial level

This could be done by evaluating genomic information and obtaining it in pure form in wet laboratory. Newly developed drug will show better results than other methods because of its specificity (Lu et al., 2020).Structure of Papain like protease (PLpro), 3-chymotrypsin-like (3Clpro) or $M^{pro}$, RNA dependent RNA polymerase, spike, helicase and all other proteins along with human ACE and type-2 transmembrane serine protease used as targets to screen Zinc-Deficiency Dermatitis Disease. Recently, these proteins were scanned in different databases, such as Chinese medicine and Indian database of Traditional Knowledge Digital Library. Also, other natural products having antiviral potential are screened with above mentioned proteins by the process of virtual ligand screening technique and the effects are recorded in clinical trials.

### 8.6 Targets for drug design

#### 8.6.1 Inhibition of human ACE-2 receptor

Four types of prominent structural proteins (Spike protein, Membrane, Nucleo capsid and Envelope protein) encoded by Coronavirus genome help in viral replication (Li S et al., 2020). Reports have suggested that abundantly present ACE-2 is the receptor for entry in target cells by COVID-19. Cryoelectron microscopic result obtained under high resolution proved the binding of ACE-2 and two spike glycoproteins having trimeric structure (Taylor et al., 2012).

There is a reported association between the binding affinity of the S-protein and ACE-2 with viral replication rate and disease severity.

The Spike protein is responsible for entry of corona virus in the host or target cell which contains large ectodomain consisting S1 and S2 subunits for receptor binding and membrane fusion respectively (Wrapp et al., 2020). Multiple host infection in COVID-19 is due to loosely attached receptor binding domain (RBD) which recognises the exopeptidases. Proteases HAT (Human airway trypsin), TMPRSS2 (Transmembrane protease serine-2) and cathepsins helps in proteolytic cleavage of spike protein (Hoffmann et al., 2020). Cleavage of S2 subunit by these protease leads to conformational changes by activating glycoprotein. Hence, begin the fusion process (Walls et al., 2020). Incorporation of viral RNA to host RNA forms Translated genome RNA in Viral replicase polyproteins i.e. *pp1a, 1ab*. Viral proteinase cleavespolyproteins into small entities known as nsps(Simmons et al., 2013).These nsps assembles in RTC (replicate transcriptase complex) for RNA synthesis, replication and transcription of subgenomic RNA's.Viral replicases are assembled in ER and Golgi complexes by vesicles and transfer to ERGIC and release of virion by vesicles get released out by exocytosis (Shereen et al., 2020).

First stage of infection is crucial for therapeutic point of view. It can be utilised to develop drugs which directly block the entry of virus. By using the structural information (amino acid sequence) in the binding region of ACE-2 receptor a suitable antibody could be searched by molecular targeting (Chakraborty, 2020).

**8.6.2 Inhibition of Main protease ($M^{pro}$)**

Polyproteins *pp1a* and *pp1ab* are synthesized with molecular weights 486 and 790 KDa, respectively and produce 16nsps by proteolytic cleavage. Involved proteases are main proteinase ($M^{pro}$) and papain- like protease (PLpro) (Fig. 2a, c). Firstly, nsp1 and nsp2 is cleaved at N-terminal by PLpro (fig 2b). $M^{pro}$ cleaves replicase polyprotein at 11 sites and produce 11 nspsare releasedfor replication(Jin et al., 2020).These polypeptides are enzymes, RNA dependant RNA polymerase, helicase and other nsps as well as accessory proteins.

**8.6.3 Inhibition of Papain like protease**

Replicase intermediates of coronavirus and other processing products assemble on intracellular membranes. Double membrane vesicles (DMVs) are formed where viral RNA is synthesized. Proteolytic processing of coronavirus replicase polyprotein is an essential step to generate functional replication complex. Therefore, Papain protease is also important target (Morse et al., 2019). SARS-CoV encodes only one functional papain like protease (PLpro) (Wu et al., 2020). It processes amino terminal of replicase polyprotein and generate 2-3 replicase products (Barretto et al., 2005). These are regulated through ubiquitation by E3 ligase. PLpro domain is present within (non-structural protein 3) nsp3.

PLpro has deubiquitinase and deISGylating activity other than its proteolytic processing activity (Barretto et al., 2005). Cell trafficking, DNA repair, and signalling is important for cellular development and is also a key player in cell cycle control, i.e. degradation of cyclins and cyclin dependent kinase inhibitor proteins. Deubiquitinating enzymes (DUBs) cleave amide, isopeptide and peptide bonds (Báez-Santos et al., 2015). It provides site for therapeutic target due to its multiple functionality (Arya et al., 2020).

**8.6.4 Inhibition of RNA dependent RNA polymerase (RdRp)**

RNA dependent RNA polymerase of SARS CoV-2 also known as nsp12 plays vital role in replication and transcription andis highly homologous to the nsp12 of SARS CoV (Yin et al., 2020). The C terminus contains RNA dependent RNA polymerase domain with a conservedsequence (Ser-Asp-Asp motif). A different type of nsp that is, nsp14 is confirmed in both SARS CoV and SARS CoV-2, having exonuclease activity (ExoN) and proof reading function. ExoN increase functioning of RNA synthesis and allow correction of nucleotide incorporation activity of RdRp. (Wu et al., 2020).

For these reasons nsp14 (ExoN) provide target site for therapeutics. Nsp14 inhibition will decrease replication fidelity by 21 folds (Pachetti et al., 2020). Involvement of other nsp7 and nsp8 in making of RNA dependent RNA polymerase (RdRp) supercomplexhas been observed (Rohaim et al., 2021). Function of Nsp8 is synthesis of up to six nucleotides. It acts as primer for nsp12 RNA synthesis. The complex formed by nsp7-nsp8 increases chance of nsp12 binding (Gao et al., 2020). Interaction between SARS CoV-2 nsp

12 with this complex is under examination. Inhibition of nsp12-RdRp complex could not cause any toxicity because its target is not available in host. Moreover, lesser side effects on host cells makes it effective target.

**8.6.5 Inhibition of helicase**

Helicase have same function in virus and prokaryotes and eukaryotes. Multifunctional helicase enzyme separates double stranded nucleic acid (NA), unwinds double-stranded DNA and RNA in the 5′→ 3′ direction and utilises free energy generated from Nucleoside triphosphate (NTP) (Wu et al., 2020). This energy generated due to hydrolysis of Nucleotide Triphosphate during translocation of single stranded nucleic acid. Helicases are involved in several biological processes. It plays key role in genome replication, recombination of proteins attached to Nucleic acids, displacement of proteins and chromatin remodelling etc (Keum and Jeong, 2012).Computational analysis predicts helicase as conserved amino acid sequence. Hence, SARS CoV-2 might have the homologous helicase. SARS CoV helicase contains almost 601 amino acids. It is a cleaved product of *pp1ab* and contains two distinct domains. Drug as helicase inhibitor might help in control of infections by virus. Searches are restricted due to unavailability of possible drugs as helicase inhibitor.

**Table 1. Table showing target of SARS CoV-2, the natural product from different plant sources which can potentially bind and inhibit those targets.**

| Targets | Natural products | Source |
|---|---|---|
| Immunomodulatory products | Astragalus polysaccharide<br>Epigallocatechin gallate<br>Resveratrol | Astragalus membranaceus<br>Extracted from green tea<br>Red wine and grapes. |
| Multiple Targets | Baicalin (3CLpro and ACE2)<br>Quercetin (3CLpro and ACE2) | Roots of Huangqin Fagopyrum, Ginkgo biloba |
| Mpro (3CLpro) | Betulinic acid (BA)<br>Berberine<br>β-Glusterol | Triterpenoid-active compound<br>European barberry,<br>Goldenseal<br>Various vegetable oils and nuts |
| RdRp | Cordycepin<br>Curcumin | Cordyceps militaris<br>Rhizomes of Curcuma longa |
| Non-structural protein | Myricetin | Grapes,Myrica rubra, and tea |
| host cell receptors ACE2/FURIN | nicotianamine, 1-methylisoguanosine, and chlorogenic acid | Glycine max,<br>Lonicera japonica |
| FURIN | Honokiol | root of Houpoea officinalis |

### 3.1 Vaccines

Earlier computational studies have indicated the presence of potential epitopes within the SARS-CoV-2 glycoprotein. Consequently, scientists have undertaken recent efforts to create vaccine candidates centered on these epitopes for combating SARS-CoV-2.

In the current investigation, we utilized advanced predictive methods to identify highly promising B and T cell epitopes within the SARS-CoV-2 glycoprotein. Subsequently, we selected the most optimal epitopes to construct a top tier multi-epitope vaccine candidate. Notably, this vaccine formulation incorporates two epitopes with the potential to elicit immune responses specifically targeting the receptor-binding motif (RBM) of SARS-CoV-2, which is chiefly responsible for viral entry into human cells. Additionally, it includes four epitopes that may orchestrate of the SARS-CoV-2 receptor-binding domain (RBD).

#### 3.1.1 The Impact of Evolving SARS-CoV-2 Mutations and Variants on COVID-19 Vaccine

Current evidence suggests that COVID-19 vaccines perform well against SARS-CoV-2 variants. They offer good protection against the alpha variant and some protection against beta and delta variants due to strong immune responses generated. Booster shots with mRNA vaccines can also help against omicron. Vaccines remain effective in preventing severe disease and hospitalization. Adaptations may not be needed for existing variants, but strategies are in place to modify vaccines if necessary. Data gaps exist, including understanding other protective factors besides antibodies and the role of T-cell responses overtime, which are crucial for dealing with current and future variants. Continued preventive measures are recommended, especially with the highly transmissible omicron variant.

#### 3.1.2 SARS CoV:

The world overcame with SARS CoV infection and it was completely under controlled in 2003. But effective vaccines are necessary for any kind of further outbreak in future. Live attenuated vaccines were designed and used. The second type of vaccine is protein cage nanoparticleswhich are designed particularly for that type of coronavirus. Receptor-binding domain based vaccines are under development against SARS CoV.

#### 3.1.3 MERS CoV:

MERS CoV vaccines may be evaluated for SARS-CoV-2 infected patients. Recombinant Modified Vaccinia virus Ankara (MVA) vaccine which expresses spike protein full length induced specific neutralizing antibody action is very specific for immune response. Elicit specific interferon-gamma which produces CD8+ in reaction against viral infection (Arabi et al, 2020).

Adenovirus type 5 (AD-d5) vaccine induces systemic and mucosal antigen-specific immunity. T cell mediated response observed. RBD subunit based vaccine- MERS CoV- RBD protein 1, in which immune response of fragment from Spike protein of virus was examined (Arabi et al., 2020). Ex-mAb YS110 is human monoclonal antibody which can bind to RBD receptor. Antibodies generated this way are known to block MERS CoV-RBD binding to its receptor of spike protein.

Adjuvants associated to MERS-CoV vaccine increased response than previous one. Adjuvants suggested to be used are MF59 and alum in MERS CoV subunit vaccine. Adjuvants application is favored, as they elicit antigen-specific antibodies as well as cell mediated responses (Arabi et al., 2020).

#### 3.1.4 SARS CoV-2:

At present it is of international concern to obtain effective vaccines to check number of escalating cases and fatalities (Simmons et al., 2020). Important vaccination requires live attenuated vaccines which proved useful in SARS. Maybe using same vaccine might help few patients, but not known. Innate immunomodulers can be used, which have high ability against viral replication. Immunomodulators such as rhesus defensin 1 and protein cage nano particles are used in vaccine development.

The vaccines which are under development can also be modified for other Coronaviruses. Vaccines developed using following strategies like- Viral vector vaccination, recombinant protein and viral like particles can be modified for different uses (Shen et al., 2010). Plasma therapy might be helpful from the people who are recovered from COVID-19 and have antibodies (Robinson, 2020). These antibodies can inhibit viral entry receptor (viral-cell receptor). This step will not allow any further fusion or viral replication in host cell. If more than one type of monoclonal antibodies is available, then fast response is expected. Other optioncould be using peptides targeting different regions of S domain. Such peptides are

HP2P-M2 peptide used in viral infections which can be useful. RBD vaccines are being evaluated for the same purpose (Le et al., 2020).

**4. Herbal Therapeutics**

**NAOQ19-** Certain Ayurvedic herbs and compounds exhibit antiviral properties against SARS-CoV-2 and can be employed in COVID-19 management. Notably, the polyherbal formulation NAOQ19, comprising 19 ingredients from 13 herbs, has demonstrated efficacy against SARS-CoV-2 in both in vitro and in vivo studies, featuring potent antivirals and immunomodulators.

Results from a meta-analysis indicate that the combined use of Traditional Chinese and Western Medicine significantly outperformed treatment with Western medicine alone.

PAFYY, a Chinese herbal remedy with a record against respiratory viruses, exhibits promising binding to SARS-CoV-2-RBD and hACE2 receptors in molecular docking studies. Yet, additional in vivo validation is essential to affirm its efficacy in preventing COVID-19, including evaluating benefits and pharmacokinetics.

**5. Synthetic drugs**

Synthetic drugs are prepared to target specific site which ultimately inhibits the viral entry or control them before replication in host body. These drugs and therapy are classified in the following categories-

**5.1 ACE-2 (Angiotensin Converting enzyme-2) Inhibitors**

The Spike protein of SARS CoV-2 attach to ACE-2 receptor for entry into host cell. ACE inhibitors are usually used for treatment of kidney dysfunction and hypertension for ACE-2 receptor (Fig. 3).

**5.1.1 Chloroquine and Quensyl-**

It is a derivative of hydroxylchloroquine. Other marketing names are Plaquenil, Hydroquin, Quinoric or Dolquine etc used in malaria and autoimmune disorders. Chloroquine phosphate inhibits ACE-2 terminal phosphorylation whereas hydroxychloroquine increases endosomal pH which is involved in viral entry in hosts (Yao et al., 2020). Hydrochloroquine drug treatment needs regulation (Lu et al, 2020).

**5.1.2 Combination therapeutic (cepharanthine, selamectin and mefloquine)**:

Cepharanthine is an alkaloid with anti-inflammatory function and derivedfrom Hayata (*Stephania cepharantha*). Selamectin shows parasiticide and anti-helminthic used as veterinarymedicine. It is derived from *Streptomyces avermitilis*. This combination was tested on panglion coronavirus for inhibition of S protein which is 92% similar to SARS CoV-2. Experiments suggest further analysis of this combination against SARS-C0V-2 (Fan et al., 2020).

**5.1.3 Drugs under invigilation against SARS CoV-2:**

Peptide inhibitor enzymes were developed after the investigation showed ACE-2 as receptor for viral attack. Several peptides and tripeptides are developed for ACE-2 inhibition of human cells. Synthetic molecules are prepared as ACE-2 inhibitors. Example: MLN-4760, N-(2-aminoethyl)-1 aziridine- ethanamine (Nami et al., 2020) and TFN-α converting enzyme (TACE) marketed as TAPI-2 block the binding are being investigated. Nicotinanamine, a phytochemical product acts as metal chelator and present in the higher plants such as soyabean is examined as strong ACE-2 inhibitor (Takahashi et al., 2015). Human recombinant soluble ACE-2 with two-way mechanism against SARS-CoV-2 is under radar. It neutralizes virus by binding to spike protein and protects organs due to regular functioning of renin-angiotensin system (Zoufaly et al., 2020).

**5.2 Replication inhibitors, membrane and assembly inhibitors for SARS-CoV-2:**

**5.2.1 Lopinavir/ritonavir (Kaletra):**

Lopinavir is the drug against HIV (Human immunodeficiency virus which inhibits HIV protease necessary for assembly of human immunodeficiency virus inside the cells. SARS CoV-2 Patients treated with this combination showed milder symptoms and reduced viral fever and chest radiographs (Chu et al., 2015). For SARS CoV-2 trial, 199 patients in China were administered with drug but results were disappointing (Cao et al., 2020). New combinations are under trail (Chu et al., 2020).

**5.2.2 Umifenovir (Arbidol):**

Ethyl-6-bromo-4-[(dimethy-lamino) methyl]-5-hydroxy-1-methyl-2(phenylsulfanylmethyl) indole -3-carboxylateis derivative of indole, small molecule manufactured in Russia are under trails (Jin et al., 2020). It inhibits clathrin-mediated endocytosis and

prevents viral host interaction. It could inhibit some global pathogenic virus i.e. hepatitis B, hepatitis C, Ebola virus herpes virus etc, which proves it to be abroad spectrum drug.

**5.2.3 Remdesivir/(GS-5734):**

Remdesivir is antiviral drug metabolised in active form which proved effective against Ebola virus and shows antiviral activity against viruses with single stranded RNA (Warren et al., 2016). It obstructs the function of RNA polymerase of virus which helps in embracingexoribonuclease for proof reading and led to inhibition of RNA synthesis. As a result depletion in Viral RNA level is obtained in vitro. It has been tested against MERS (Gordon et al., 2020). China initiated usage of Remdesivir which is now used in USA, Singapore, France Taiwan and several other countries. Galidesivir, Simeprevir, Filibuvir, Cepharanthine, Tegobuvir and Ribavirin are other drugs for RdRp inhibition.

**5.2.4 Favipiravir (Avigan):**

It is pyrazine carboxamide derivative and guanine analogue which inhibits RNA dependent RNA polymerase (RdRp) and causes toxic mutations (Furuta et al., 2017).It Inhibit viral replication in large quantity. It is a helpful drug in yellow fever, West Nile virus and Ebola virus. New combinations are under invigilation such as combined with monoclonal antibody or with chloroquine phosphate etc.

**5.3 $M^{pro}$protease Inhibitor**

**5.3.1 α- ketoamide 13b**

$M^{pro}$ forms the protease of betacoronavirus which is necessary for translation of polyproteins from viral RNA. 13a and 13b are pyridine containing- alpha-ketoamides which showed acceptable results when tested on mice (Zhang et al., 2020). Nebulized 13b administration displays better results and reside in lungs for longer time and maintain high concentration.

**5.3.2 N3 (Michael acceptor inhibitor)-**

Virtual drug designing used for creation of similar synthetic drug such as N3 (Jin et al., 2020). Another molecule is Michael acceptor inhibitor, useful in COVID-19 and MERS CoV for $M^{pro}$ inhibition. Two Michael acceptor inhibitors B1 and B2 designed similar to N3 are able to bind at active site of Mpro (Arafet et al., 2020).

**5.3.3 Boceprevir-**

It is a β- ketoamide inhibitor and Hepatitis C protease inhibitor. Boceprevir and narlaprevir showed high affinities for Mpro based on the structural analysis. There have been tudies related to its enzyme kinetics which demonstrate micromolar inhibition of Mpro (Kneller et al., 2020).

**5.4 Inhibiter of TMPRSS2**Host cell proteases are involved in activation of envelope glycoproteins. Transmembrane protease/ inhibitors subfamily member2 helps spike protein in fusion and entry of virus through receptor. SARS CoV-2 and SARS CoV both have the similar kind of protease (Dwight et al., 2020).

**5.4.1 Serine Protease inhibitors-**

Drug marketed as Foipan [FOY-305 (Camostat)] consist synthetic serine protease inhibitor Camostatmelisate, (NI-03) is alternative name for drug, developed years ago for different types of carcinoma, exocrine pandemic inhibition etc (Yamaya et al., 2015).Approved drug 4-(2-Aminomethyl) benzenesulfonyl fluoride hydrochloride is a serine protease which also showed different levels of anti-viral activities (Li et al., 2017). FUT-175 (Buipel) is an approved synthetic serine protease inhibitor and it was found useful inhibiting TMPRSS-2 protease activity in MERS CoV. TMPRSS-2 could be useful inhibition site in SARS CoV-2 (Hussman et al., 2020).

**5.4.2 Others-**

Bromhexine hydrochloride drug could be used for TMPRSS2 inhibition. It is an ingredient in a mucolytic cough suppressant. Nafamostatmesliate could be used for SARS CoV-2 as it shares homologous amino acid sequence with MERS CoV. Nafamostatmelisate in phase-2 clinical trial was found effective with limited side effects.

## 6. Plants, herbs and natural compounds as therapeutics

Natural compounds and phytochemicals can inhibit viral infections at different stage of infection. Many naturally occurring products are capable to hinder viral replication and possess wide-spectrum of anti-viral effects. Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 3 (NLRP3) is an intracellular

sensor, detects viral cells and motifs, release signals and act as natural irritant which activate NLRP3 inflammasome. Respiratory problems associated with SARS CoV due to NLRP3 inflammasome. Activated macrophagers and T-helper cells contain NLRP3 inflammasome and escalate number of inflammatory cytokines.

Stilbenoid a polyphenol found naturally in (*Vitis vinifera*) wine grapes and sprouted peanuts (*Arachis hypogaea*) in higher concentration. Resveratrol (trans-3,5,4′-trihydroxystilbene) ismarketing name for this polyphenol. It inhibited MERS CoV nucleocapsid protein *in-vitro* and cell apoptosis and hinder viral replication which can be utilised in COVID-19.

Some of the flavonoids having good response against coronavirus are myricentin, quercetin, baicalin, leutiolin etc. They act against viral infections in different mechanisms and present as supplements.

A Chinese herb also found useful for infection treatment manufactured by name Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) (Ho et al., 2007). Being an anthraquinone compound shown to inhibit ACE-2 receptor and SARS CoV-2 spike protein interaction.

## 7. Conclusion

The Coronavirus outbreak in recent years has challenged the healthcare of whole world. It is a threat to whole mankind, killing millions of people in just one emergence. Last year World experienced horrifying spread of COVID-19. Somehow countries managed to provide testing kits but data obtained were initially non-reliable due to unattended cases. It was not possible to provide vaccination to such a large population in short span of time but few companies increased the pace. Available vaccines can prevent infection mortality but how much these vaccines could be beneficial is still unknown. With new variants appearing several times one cannot rely only on immunity boosters. Moreover, drugs are necessary for treatment after infection. Switching to drugs development is necessary, which are either approved, under investigation or novel drugs for future use. These drugs designed mainly to target enzymes involved inreceptor- viral binding site, viral replication, viral assembly and degradation of viral envelope. Viral enzyme could be used to develop effective drugs which are involved in metabolic activities of Coronavirus. It should be kept in mind that the designed drug or vaccine focus not only current situation but also for future pandemics. The prepared synthetic drugs against disease are beneficial for disease control but have several side effects which can be dangerous. In this case scientist often bend towards natural metabolites and compounds. A variety of natural compounds are available that can be used to develop antiviral compounds. Drug development either by synthetic mode or natural metabolite requires validation and different levels of clinical trials. Due to lack of time, we cannot skip the steps in novel drugs. It is a very critical situation we all are facing.

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## References

1. **Arabi, Y., Shalhoub, S., Mandourah, Y., Al-Hameed, F., Al-Omari, A., Al-Qasim, E., Jose, J., Alraddadi, B., Almotairi, A., Al-Khatib, K., Abdulmomen, A., Qushmaq, I., Sindi, A.A., Mady, A., Solaiman, O., Al-Raddadi, R., Maghrabi, K., Ragab, A., Al-Mekhlafi, G.A., Balkhy, H.H., Al-Harthy, A., Kharaba, A., Gramish, J.A., Al-Aithan, A.M., Al-Dawood, A., Laura Merson, L., Hayden, F.G., Fowler, R.,** 2020. Ribavirin and interferon therapy for critically ill patients with Middle East Respiratory Syndrome: a multicenter observational study. *Clin. Infect. Dis.* 70(9), 1837–1844. doi: 10.1093/cid/ciz544.
2. **Arafet, K., Serrano-Aparicio, Na., Lodola, A., Mulholland, A.J., González, F.V., Świderek, K., Moliner, V.,** 2020. Mechanism of inhibition of SARS-CoV-2 Mpro by N3 peptidyl Michael acceptor explained by QM/MM simulations and design of new derivatives with tunable chemical reactivity. *Chemical Science* 12(4), 1433-1444. doi:10.1039/D0SC06195F.
3. **Arya, R., Kumari, S., Pandey, B., Mistry, H., Bihani, S.C., Das, A., Prashar, V., Gupta, G.D., Panicker, L., Kumar, M.,** 2021. Structural insights into SARS-CoV-2 proteins. *J. Mol. Biol.* 433, 166725. https://doi.org/10.1016/j.jmb.2020.11.024
4. **Astuti, I., Ysrafil,** 2020. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. *Diabetes Metab Syndr* 14(4), 407-412. https://doi.org/10.1016/j.dsx.2020.04.020.
5. **Báez-Santos, Y.M., John, S.E.St., Mesecar, A.D.,** 2015. The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds. *Antiviral Research*. 115, 21-38. https://doi.org/10.1016/j.antiviral.2014.12.015.
6. **Bai, Y., Yao, L., Wei, T., Tian, F., Jin, D.Y., Chen, L., Wang, M.,** 2020. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA* 323(14),1406-1407. doi: 10.1001/jama.2020.2565.
7. **Barretto, N., Jukneliene, D., Ratia, K., Chen, Z., Mesecar, A.D., Baker, S.C.,** 2005. The Papain-Like Protease of Severe Acute Respiratory Syndrome Coronavirus Has Deubiquitinating Activity. *Journal of Virology*. 79 (24), 15189-15198. DOI: 10.1128/JVI.79.24.15189-15198.2005
8. **Bauch, C.T., Lloyd-Smith, J.O., Coffee, M.P., Galvani, A.P.,** 2005. Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future. *Epidemiology*. 16, 791-801. doi: 10.1097/01.ede.0000181633.80269.4c.
9. **Belouzard, S., Chu, V.C., Whittaker, G.R.,** 2009. Activation of the SARS coronavirus spike protein via

sequential proteolytic cleavage at two distinct sites. Proceedings of the National Academy of Sciences 106 (14), 5871-5876. DOI: 10.1073/pnas.0809524106

10. **Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., Yuan, Y., Chen, H., Li, H., Huang, H., Tu, S., Gong, F., Liu, Y., Wei, Y., Dong, C., Zhou, F., Gu, X., Xu, J., Liu, Z., Zhang, Y., Li, H., Shang, L., Wang, K., Li, K., Zhou, X., Dong, X., Qu, Z., Lu, S., Hu, X., Ruan, S., Luo, S., Wu, J., Peng, L., Cheng, F., Pan, L., Zou, J., Jia, C., Wang, J., Liu, X., Wang, S., Wu, X., Ge, Q., He, J., Zhan, H., Qiu, F., Guo, L., Huang, C., Jaki, T., Hayden, F.G., Horby, P.W., Zhang, D., Wang, C.,** 2020. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *New England Journal of Medicine*. 382, 1787-1799. doi: 10.1056/NEJMoa2001282.

11. **Chakraborty, K., Chatterjee, M.,** 2020. Psychological impact of COVID-19 pandemic on general population in West Bengal: A cross-sectional study. *Indian Journal of Psychiatry*. 62(3), 266-272. 10.4103/psychiatry.IndianJPsychiatry_276_20.

12. **Chu, C.M., Cheng, V.C.C., Hung, I.F.N., Wong, M.M.L., Chan, K.H., Chan, K.S., Kao, R.Y.T.,Poon, L.L.M., Wong, C.L.P., Peiris, J.S.M., Yuen, K.Y.,** HKU/UCH Sars Study group. 2004. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax.* 59, 252-256. DOI: 10.1136/thorax.2003.012658

13. **Dierynck, I., Van Marck, H., Van Ginderen, M., Jonckers, T.H., Nalam, M.N., Schiffer, C.A., Raoof, A., Kraus, G., Picchio, G.,** 2011. TMC310911, a novel human immunodeficiency virus type 1 protease inhibitor, shows in vitro an improved resistance profile and higher genetic barrier to resistance compared with current protease inhibitors. *Antimicrob*. Agents Chemother. 55, 5723-5731. DOI: 10.1128/aac.00748-11

14. **Dwight, L.M., Sternberg, A., Stange, U., Laufer, S., Naujokat, C.,** 2020. Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacological Research*. 157, 104859. https://doi.org/10.1016/j.phrs. 2020.104859.

15. **Fan, H.H., Wang, L. Q., Liu, W.L., An, X.P., Liu, Z.D., He, X.Q., Song, L.H., Tong, Y.G.,** 2020. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. *Chinese medical journal*. 133(9), 1051–1056. https://doi.org/10.1097/CM9.0000000000000797.

16. **Fan, H.H., Wang, L.Q., Liu, W.L., An, X.P., Liu, Z.D., He, X.Q., Song, H.L., Tong, Y.G.,** 2020. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a2019- novel coronavirus (2019-nCoV) related coronavirus model. *Chin. Med. J. (Engl.)* 133 (9), 1051-1056. https://doi.org/10.1097/CM9.0000000000000797.

17. **Furuta, Y., Gowen, B.B., Takahashi, K., Shiraki, K., Smee, D.F., Barnard, D.L.**, 2013. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Antiviral Res*. 100(2), 446-454. https://doi.org/10.2183/pjab.93.027.

18. **Gao, Y., Yan, L., Huang, Y., Liu, F. Zhao, Y., Cao, L., Wang, T., Sun, Q., Ming, Z., Zhang, L., Ge, J., Zheng, L., Zhang, Y., Wang, H., Zhu, Y., Zhu, C., Hu, T., Hua, T., Zhang, B., Yang, X., Li, J., Yang, H., Liu, Z., Xu, W., Guddat, L.W., Wang, Q., Lou, Z., Rao, Z.,** 2020. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science*. 368 (6492), 779-782. DOI: 10.1126/science.abb7498.

19. **Gordon, C.J., Tchesnokov, E.P., Woolner, E., Perry, J.K., Feng, J.Y., Porter, D.P., Götte, M.,** 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J. Biol. Chem*. 295, 6785–6797. https://doi.org/10.1074/jbc.RA120.013679.

20. **Gralinski, L.E., Menachery, V.D.,** 2020. Return of the coronavirus: 2019-nCoV. *Viruses*. 12 (2), 135. doi: 10.3390/v12020135.

21. **Guan, Y., Zheng, B.J., He Y.Q., Liu, X.L., Zhuang, Z.X., Cheung, C.L., Luo, S.W., Li, P.H., Zhang, L.J., Guan, Y.J., Butt, K.M., Wong, K.L., Chan, Lim, W., Shortridge, K.F., Yuen, K.Y., Peiris, J.S.M., Poon, L.L.M.,** 2003. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*. 2003; 302: 276-8. DOI: 10.1126/science.1087139.

22. **Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D.S.C., Du, B., Li, L., Zeng, G., Yuen, K.Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., Li, S., Wang, J., Liang, Z., Peng, Y., Li, W., Yong, L., Hu, Y., Peng, P., Wang, J., Liu, J., Chen, Z., Li, G., Zheng, Z., Qiu, S., Luo, J., Ye, C., Zh, S., Nanshan, Z.,** 2020. Clinical characteristics of 2019 novel coronavirus infection in China. *MedRxiv*. https://doi.org/10.1101/2020.02.06.20020974.

23. **Harapan, H., Naoya, I., Amanda, Y., Wira, W., Synat, K., Haypheng, T., Dewi, M., Zinatul, H., Abram, L.W., Mudatsir, M.,** 2020. Coronavirus disease 2019 (COVID-19): A literature review. *Journal of infection and Public Health*. 13(5), 667–673. doi: 10.1016/j.jiph.2020.03.019.

24. **Ho, T.Y., Wu, S.L., Chen, J.C., Li, C.C., Hsiang, C.Y.,** 2007. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Res*. 74, 92–101. https://doi.org/10.1016/j.antiviral.2006.04.014.

25. **Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Müller, M.A., Drosten, C., Pöhlmann, S.,** 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271-280. https://doi.org/10.1016/j.cell.2020.02.052.

26. **Holshue ML, DeBolt C, Lindquist S., Lofy, K.H., Wiesman, J., Bruce, H., Spitters, C., Ericson, K., Wilkerson, S., Tural, A., Diaz, G., Cohn, A., Fox, L., Patel, A., Gerber, S.I., Kim, L.,Tong, S., Lu, X., Lindstrom, S., Pallansch, M.A., Weldon, W.C., Biggs, H.M., Uyeki, T.M., Pillai, S.K.,** Washington State 2019-nCov Case Investigation Team. 2020. First Case of 2019 Novel Coronavirus in the United States. *N. Engl. J. Med.* 382, 929-936. doi: 10.1056/NEJMoa2001191.

27. **Hussman, J.P.,** 2020. Cellular and Molecular Pathways of COVID-19 and Potential Points of Therapeutic Intervention. *Frontiers in Pharmacology*. 382(10), 929-936. DOI-10.3389/fphar.2020.01169

28. **Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., Yang, X., Bai, F., Liu, H., Liu, X., Guddat, L.W., Xu, W., Xiao, G., Qin, C., Shi, Z., Jiang, H., Rao, Z., Yang, H.,** 2020. Structure of $M^{pro}$ from SARS-CoV-2 and discovery of its inhibitors. *Nature*. 582(7811), 289–293 (2020). https://doi.org/10.1038/s41586-020-2223-y.

29. **Keum, Y.S., Jeong, Y.J.,** 2012. Development of chemical inhibitors of the SARS coronavirus: Viral helicase as a potential target. *Biochem. Pharmacol.* 84, 1351–1358. https://doi.org/10.1016/j.bcp.2012.08.012

30. **Khan, S., Peng, L., Siddique, R., Nabi, G., Nawsherwan, X.M., Liu J., Han, G.,** 2020. Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. *Infection Control and Hospital Epidemiology*, 41(6), 748-750. doi:10.1017/ice.2020.84.

31. **Kneller, D.W., Galanie, S., Phillips, G., O'Neill, H.M., Coates, L., Kovalevsky, A.,** 2020. Malleability of the SARS-CoV-2 3CL Mpro Active-Site Cavity Facilitates Binding of Clinical Antivirals. *Structure*, 28(12), 1313-1320. doi: 10.1016/j.str.2020.10.007.

32. **Le, T.T., Andreadakis, Z., Kumar, A., Román, R.G., Tollefsen, S., Saville, M., Mayhew, S.,** The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*19(5), 305-306. doi: 10.1038/d41573-020-00073-5.

33. **Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S.M., Lau, E.H.Y., Wong, J.Y., Xing, X., Xiang, N., Wu, Y., Li, C., Chen, Q., Li, D., Liu, T., Zhao, J., Liu, M., Tu, W., Chen, C., Jin, L., Yang, R., Wang, Q., Zhou, S., Liu, H., Luo, Y., Liu, Y., Shao, G., Li, H., Tao, Z., Yang, Y., Deng, Z., Liu, B., Ma, Z., Zhang, Y., Shi, G., Lam, T.T.Y., Wu, J.T., Gao, G.F., Cowling, B.J., Yang, B., Leung, G.M., Feng, Z.,** 2020. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N. Engl. J. Med.* 382(13):1199-1207. doi:10.1056/NEJMoa2001316.

34. **Li, S., Tang, Z., Li, Z., Liu, X.,** 2020. Searching therapeutic strategy of new coronavirus pneumonia from angiotensin-converting enzyme 2 : the target of COVID-19 and SARS-CoV. *European Journal of Clinical Microbiology & Infectious Diseases*. 39,1021–1026. https://doi.org/10.1007/s10096-020-03883-y.

35. **Li, W.S., Hui, J.M., Wu, Y.L., Tanaka, Y., Zhang, W.,** 2017. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. *Biochimie.* 142, 1-10. https://doi.org/10.1016/j.biochi.2017.07.016.

36. **Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., Wang, M.,** 2020. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *CellDiscov.* 6, 16. doi: 10.1038/s41421-020-0156-0.

37. **Lu, R., Wilson, X., Overton, J.L., Yu, S., Chiamvimonvat, N., Thai P.N.,** 2020. Assessment of Chloroquine and Hydroxychloroquine Safety Profiles: A Systematic Review and Meta-Analysis. *Frontiers in Pharmacolog*.11, 1584. DOI-10.3389/fphar.2020.562777

38. **Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhou, L., Chen, J., Meng, Y., Wang, J., Lin, Y., Yuan, J., Xie, Z., Ma, J., Liu, W.J., Wang, D., Xu, W., Holmes, E.C., Gao, G.F., Wu, G., Chen, W., Shi, W., Tan, W.,** 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet.* 395(10224), 565-574. https://doi.org/10.1016/S0140-6736(20)30251-8

39. **Morse, J.S., Lalonde, T., Xu, S., Liu, W.R.,** 2020. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem*. 21 (5), 730–738. DOI: 10.1002/cbic.202000047.

40. **Mourya, D.T., Sapkal, G., Yadav, P.D., Belani, S.K.M., Shete, A., Gupta, N.,** Biorisk assessment for infrastructure and biosafety requirements for the laboratories providing coronavirus SARS-CoV-2/(COVID-19) diagnosis. *Indian J. Med. Res.* 151(2&3), 172-176. doi: 10.4103/ijmr.IJMR_763_20.

41. **Nami, B., Ghanaeian, A., Ghanaeian, K., Nami, N.,** 2020. The Effect of ACE2 Inhibitor MLN-4760 on the Interaction of SARS-CoV-2 Spike Protein with Human

ACE2: A Molecular Dynamics Study. *ChemRxiv*. Preprint. https://doi.org/10.26434/chemrxiv.12159945.v1

42. **Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., Masciovecchio, C., Angeletti, S., Ciccozzi, M., Gallo, R. C., Zella, D., Ippodrino, R.,** 2020. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *Journal of translational medicine*. 18(1), 179. https://doi.org/10.1186/s12967-020-02344-6.

43. **Phan, L.T., Nguyen, T.V., Luong, Q.C., Nguyen, T.V., Nguyen, H.T., Le, H.Q., Nguyen, T.T., Cao, T.M.,** Pham, Q.D., 2020. Importation and human-to-human transmission of a novel coronavirus in Vietnam. *N. Engl. J. Med.* 382(9), 872-874. doi: 10.1056/NEJMc2001272.

44. **Robinson, J.,** 2020. Ten things pharmacists should know about COVID-19 vaccines, Vaccination. *The Pharmaceutical Journal*. DOI:10.1211/PJ.2020.20208051

45. **Rohaim, M. A., El Naggar, R. F., Clayton, E., &Munir, M.,** 2021. Structural and functional insights into non-structural proteins of coronaviruses. *Microbial pathogenesis*. 150, 104641. https://doi.org/10.1016/j.micpath.2020.104641

46. **Sarkar, C., Mondal, M., Torequl, I.M., Martorell, M., Docea, A.O., Maroyi, A., Sharifi-Rad, J., Calina, D.,** 2020. Potential Therapeutic Options for COVID-19: Current Status, Challenges, and Future Perspectives. Frontiers in Pharmacology, 11, DOI-10.3389/fphar.2020.572870.

47. **Shen, L.W., Mao, H.J., Wu, Y.L., Tanaka, Y., Zhang, W.,** 2017. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. Biochimie. 142, 1–10. https://doi.org/10.1016/j.biochi.2017.07.016.

48. **Shereen, M.A., Khan, S., Kazmic, A., Bashira, N., Siddique, R.,** 2020. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*. 24, 91–98. https://doi.org/10.1016/j.jare.2020.03.005.

49. **Simmons, G., Zmora, P., Gierer, S., Heurich, A., Pöhlmann, S.,** 2013. Proteolytic activation of the SARS-coronavirus spike protein: Cutting enzymes at the cutting edge of antiviral research. *Antiviral Res.* 100, 605–614. https://doi.org/10.1016/j.antiviral.2013.09.028.

50. **Sun, P, Lu, X, Xu, C, Sun, W, Pan, B.,** 2020. Understanding of COVID-19 based on current evidence. *J. Med. Virol.* 92, 548– 551. https://doi.org/10.1002/jmv.25722.

51. **Szymański, P., Markowicz, M., Mikiciuk-Olasik, E.,** 2012. Adaptation of high-throughput screening in drug discovery-toxicological screening tests. *International journal of molecular sciences*. 13(1), 427–452. https://doi.org/10.3390/ijms13010427.

52. **Takahashi, S., Yoshiya, T., Yoshizawa-Kumagaye, K., Sugiyama, T.,** 2015. Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. *Biomed. Res.* 36, 219–224. https://doi.org/10.2220/biomedres.36.219.

53. **Taylor, H.S., Gallagher, T.,** 2012. Ready, set, fuse! the coronavirus spike protein and acquisition of fusion competence. Virues 4, 557–580. https://doi.org/10.3390/v4040557

54. **Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T., Veesler, D.,** 2020. Structure, Function, and Antigenicity of the SARS CoV-2 Spike Glycoprotein. Cell Elsevier 180, 281–292. https://doi.org/10.1016/j.cell.2020.02.058.

55. **Warren, T.K., Jordan, R., Lo, M.K., Ray, A.S., Mackman, R.L., Soloveva, V., Siegel, D., Perron, M., Bannister, R., Hui, H.C., Larson, N., Strickley, R., Wells, J., Stuthman, K.S., Tongeren, S.A.V,. Garza, N.L., Donnelly, G., Shurtleff A.C., Retterer, C.J., Gharaibeh, D., Zamani, R., Kenny, T., Eaton, B.P., Grimes, E., Welch, L.S., Gomba, L., Wilhelmsen C.L., Nichols, D.K., Nuss, J.E., Nagle, E.R., Kugelman, J.R., Palacios, G., Doerffler, E., Neville, S., Ernest Carra, E., Clarke, M.O., Zhang, L., Lew, W., Ross, B., Wang, Q., Chun, K., Wolfe, L., Babusis, D., Park, Y., Stray, K.M., Trancheva, I., Feng, J.Y., Barauskas, O., Xu, Y., Wong, P., Braun, M.P., Flint, M., McMullan, L.K., Chen, S.S., Fearns, R., Swaminathan, S., Mayers, D.L., Spiropoulou, C.F., Lee, W.A., Nichol, S.T., Cihlar, T., Bavari, S.,** 2016. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 531, 381–385. https://doi.org/10.1038/nature17180

56. **WHO: Geneva, Switzerland.** Coronavirus disease 2019 (COVID-19) Situation Report – 38. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200227-sitrep-38-covid-19.pdf?sfvrsn=9f98940c_2 (Accessed on 14 November 2020).

57. **Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S., McLellan, J.S.,** Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 367(6483), 1260-1263. https://doi.org/10.1101/2020.02.07.2002115432.

58. **Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., Li, H.,** 2020. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B.* 10 (5), 766- 788. https://doi.org/10.1016/j.apsb.2020.02.008.

59. **Wu, F., Zhao, S., Yu, B., Chen, Y.M., Wang, W., Song, Z.G., Hu, Y., Tao, Z.W., Tian, J.H., Pei,Y.Y., Yuan, M.L., Zhang, Y.L., Dai, F.H., Liu, Y., Wang, Q.M., Zheng, J.J., Xu, L., Holmes, E.C., Zhang, Y.Z.,** 2020. A new coronavirus associated with human respiratory

disease in China. *Nature*. 579**,** 265–269. https://doi.org/10.1038/s41586-020-2008-3.

60. **Wu, Z., McGoogan, J.M.,** 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 323(13), 1239-1242. doi: https://doi.org/10.1101/2020.02.07.20021154.

61. **Yamaya, M., Shimotai, Y., Hatachi, Y., Kalonji, N.L., Tando, Y., Kitajima, Y., Matsuo, K., Kubo, H., Nagatomi, R., Hongo, S., Homma, M., Nishimura, H.,** 2015. The serine protease inhibitor camostat inhibits influenza virus replication and cytokine production in primary cultures of human tracheal epithelial cells. *Pulm. Pharmacol. Ther.* 33, 66–74. doi: 10.1016/j.pupt.2015.07.001.

62. **Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Nui, P., Liu, X., Zhau, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., Liu, D.,** 2020. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin. Infect. Dis.* 71(15), 732-739. https://doi.org/10.1093/cid/ciaa237.

63. **Yin, W., Mao, C., Luan, X., Shen, D.D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y.C., Tian, G., Jiang, H.W., Tao, S.C., Shen, J., Jiang, Y., Jiang, H., Xu, Y., Zhang, S., Zhang, Y., Xu H.E.,** 2020. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. *Science*. 368(6498), 1499-1504. DOI: 10.1126/science.abc1560

64. **Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., Hilgenfeld, R.,** 2020. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved αketoamide inhibitors. *Science*. 368(6489), 409-412. https://doi.org/10.1126/science.abb3405.

65. **Zhang, S., Diao, M.Y., Duan, L., Lin, Z., Chen, D.,** 2020. The novel coronavirus (SARS-CoV-2) infections in China: prevention, control and challenges. *Intensive Care Medicine*. 46, 591-593. https://doi.org/10.1007/s00134-020-05977-9

66. **Zheng J.** 2020. SARS-CoV-2: an Emerging Coronavirus that causes a Global Threat. Int. J. Biol.Sci. 16(10):1678-1685. *Doi:10.7150/ijbs.45053*

67. **Zoufaly, A., Poglitsch, M., Aberle, J.H., Hoepler, W., Seitz, T., Traugott, M., Grieb, A., Pawelka, E., Laferl, H., Wenisch, C., Neuhold, S., Haider, D., Stiasny, K., Bergthaler, A., Stoeckl, E.P., Mirazimi, A., Montserrat, N., Zhang, H., Slutsky, A.S., Penninger, J.M.,** 2020. Human recombinant soluble ACE-2 in severe COVID-19. *The Lancet Respiratory Medicine.* 8(11), 1154-1158. *doi: 10.1016/S2213-2600(20)30418-5.*