Conventional Drug Targets of Corona Virus

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Abstract- *In recent times the corona outbreak has become an epidemic disaster all over the world, lack of suitable drugs to treatment has become a major issue right now. In this regard we have searched reviewed many articles as well as research papers to identify drug targets of the coronavirus. We have seen PubMed, Elsevier with keywords like COVID19, HCoV, NCoV, CORONA VIRUS, SERCoV, MERS-CoV, etc till now. We have identified 6 suitable and effective drug targets that can be targeted and effectively used for the killing of a virus ,the 6 targets include(SPIKE PROTEIN, MEMBRANE PROTEIN, NUCLEOCAPSID PROTEIN, HEMAGGLUTIN ESTERASE, PROTEASE). Many non-structural proteins nearly 15 can also be targeted and used in drug designing purposes. One of the major drawbacks is that the coronavirus undergoes frequent recombinations. This is a negative factor for producing a vaccine in case of covid-19 attack.*

Keywords- Corona virus, Drug target, Molecule, Middle East respiratory syndrome, Severe acute respiratory syndrome, COVID-19.

I. INTRODUCTION

Coronavirus is a group of related viruses that cause disease in mammals and birds. In humans, coronavirus cause mild respiratory infections, such as some common cold cases (among other possible causes, predominantly rhinoviruses) and others that may be lethal, such as SARS, MERS, and COVID-19. Symptoms of another species vary: They cause upper respiratory tract disease in poultry, and diarrhea in cows and pigs. Coronaviruses make up the Orthocoronavirinae subfamily, in the Coronaviridae family, order Nidovirales, and realm Riboviria, they are enveloped viruses with a single-stranded RNA genome and a helical symmetry nucleocapside.Coronavirus genome size ranges from approximately 27 to 34 kilobases, the largest among known RNA viruses. The name coronavirus is derived from the Latin corona, meaning "crown" or "halo," which refers to the characteristic appearance reminiscent of the crown or solar corona around the virons (virus particles) when viewed under a two-dimensional electron microscopy, due to the surface covering of the club-shaped protein spikes.

Other members of this family have been identified since then, including SARS-CoV in 2003, HCoV NL63 in 2004, HKU1 in 2005, MERS-CoV in 2012, and SARS-CoV-2 (formerly known as 2019-nCoV) in 2019. Most of these cases involved serious respiratory infections. Coronaviruses are large spherical pleomorphic particles, with bulbous surface projections.The diameter of the virus particles is approximately 120 nm. The virus envelope in electron micrographs appears as a distinct pair of dense electron shells.The viral envelope consists of a lipid bilayer in which the membrane (M), the envelope (E) and the spike (S) structural proteins are anchored. A subset of coronaviruses (specifically the members of betacoronavirus subgroup A) also has a shorter spike-like surface protein called hemagglutinin esterase (HE).Inside the envelope is the nucleocapsid formed from multiple copies of the nucleocapsid (N) protein bound to the positive-sense single-stranded RNA genome in continuous bead-on-strand conformation. The size of the coronavirus genome ranges from approximately 27 to 34 kilobases.The lipid bilayer envelope, membrane protein, and nucleocapsid protect the virus when it is outside the host cell. These are the major drug targets for the virus.

II. REPLICATION AND TRANSMISSION

In the case of Sars-Cov, transmission is caused by Droplet infection (breathing secretions) and is close to individual–to–character contact. It can be further spread through Sweat, Stool, Urine, and Respiratory Secretions. When Virus enters the frame, it binds to the number one target cells consisting of enterocytes and pneumocytes, through setting up A Cycle of Contamination and Replication. Other Goal Cells Of Cov Are Epithelial Cells Of Renal Tubules, Tubular Epithelial Cells Of Kidney, Immune Cells, and Cerebral Neuron Cells. Cov attaches to target cells With the help of Spike Protein–Host Cell Protein Interaction (Angiotensin Converting Enzyme-2 [Ace-2] Interaction In Sars-Cov and Dipeptidyl Peptidase-4 [Dpp-4] In Mers-Cov After Receiver Recognition, Virus Genome With Its Nucleocapsid Is Released Into The Cytoplasm Of Host cells.Viral Genome Contains Orf1a And Orf1b Genes, Which Produces Two Pps That Are Pp1a And Pp1b, Which Help To Take Command Over Host Ribosomes For Their Own Translation Process Both Pp1a And Pp1b Take Part In Formation Of Replication Transcription Complex. After Processing Pp By Protease, It Produces 16 Nsps. All Nsps have their own specific functions, such as the suppression of

the host gene expression by Nsp1 and Nsp2, the formation of a multi-domain complex by Nsp3, Nsp5 which is a M protease having a role in replication, Nsp4 and Nsp6 which are transmembrane (Tm) proteins,Nsp7 and Nsp8 Which Function As A Primase, Nsp9–A Rna-Binding Protein, The Dimeric Type Of Which For Viral Infection Is Essential. Induction of Dysturbance to Dimerization of Nsp9can be a way to overcome Cov infection. Nsp10 Acts As A Cofactor For Activation Of The Replicative Enzyme. Nsp12 Shows Rna-Dependent Rna Polymerase Activity, Nsp13 Shows Helicase Activity, Nsp14 Shows Exoribonuclease Activity, Nsp15 Shows Endoribonuclease Activity, and Nsp16 Has Methyl Transferase Activity. All Nsps Have Important Role In Replication and Transcription. Synthesized Proteins such as M, E, and S Are Entered Into The Endoplasmic Reticulum (Er),Golgi Intermediate Compartment (Ergic) Complex And Make The Structure Of Viral Envelope. On The Other Hand, The Replicated Genome Binds To N Protein And Forms The Ribonucleoprotein (Rnp) Complex. The Outer Cover Is Formed By The M, E, And S Proteins.Finally, The Virus Particle Comes Out Of The Ergic By Making A Bud,Like Structure.These Mature Virions Form A Vesicle, Which Fuses With The Plasma Membrane And Releases The Virus Particles Into The Extracellular Region.The Detailed Structure Of Cov And Its Life Cycle Is Depicted In Figures 1 And 2. On Infection, The Sars-Cov and Mers-Cov cause a surge of pro-inflammatory cytokines and chemokines that cause damage to the lung tissue , And finally in some cases, lung failure. There is currently no specific antiviral drug for the treatment of cov-associated pathologies. Most strategies of treatment focus on symptomatic management and only supportive therapy. Ribavirin, interferon (IFN)α, and mycophenolic acid are under development or used off label. There are numerous newspaper articles citing the efficacy of anti-HIV drugs: ritonavir, lopinavir, either alone or in combination with oseltamivir, remdesivir, and chloroquine, among which ritonavir, remdesivir, and chloroquine showed cellular-level efficacy that further requires experimental support and approval. Since there is no well-defined therapy available that specifically targets CoV, we have reviewed potential protein structures in this article that could be potential targets for developing a therapeutic approach to CoV therapy.

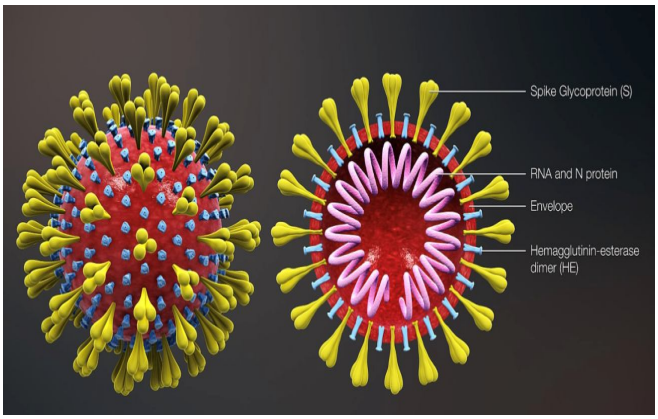

fig1 shows electron microscopic animation image of corona virus

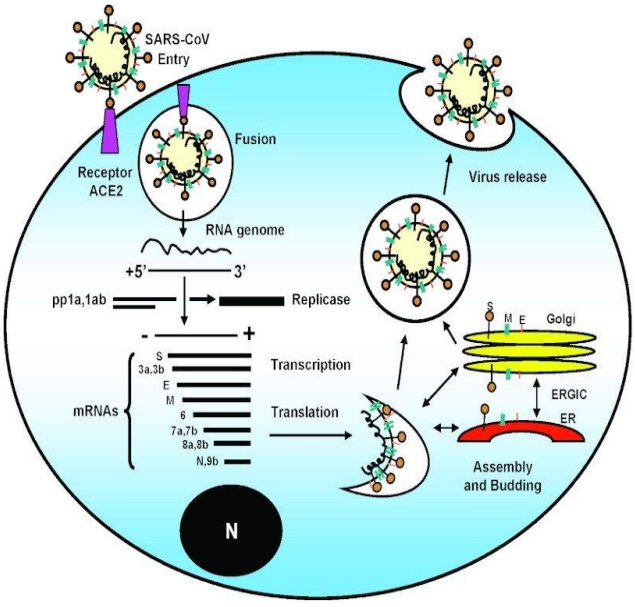

Fig2:The life cycle of CoV in host cells. The S proteins of CoV binds to cellular receptor angiotensin-converting enzyme 2 (ACE2) which is followed by entry of the viral RNA genome into the host cell and translation of structural and non structural proteins (NSP) follows. ORF1a and ORF1ab are translated to produce pp1a and pp1ab polyproteins, which are cleaved by the proteases that are encoded by ORF1a to yield 16 non-structural proteins. This is followed by assembly and budding into the lumen of the ERGIC (Endoplasmic Reticulum Golgi Intermediate Compartment). Virions are then released from the infected cell through exocytosis. S: spike, E: envelope, M: membrane, N: nucleocapsid. PP: polyproteins, ORF: Open reading frame, CoV: coronavirus

III. MATERIALS&METHODS

DATABASE SCREENING:

We screened PubMed and RCSB databases with keywords HCoV, NCoV, coronavirus, SERS-CoV, MERS-

CoV, 2019-nCoV, crystal structure, X-ray crystallography structure, NMR structure, target and drug target until 2020. Database files were extracted using the endnote, and the title and abstract screening was performed using Rayyan QCRI. Full text of these screened articles was further screened for possible inclusion in the systematic review. Articles that assessed different CoV drug-gable targets and assessed different targets some more targets were included.

IV. RESULTS&DISSCUSSION

A total of 394 articles were identified following a preliminary assessment of the databases. A total of 230 articles were excluded after the title and abstract screening. Full-text screening of the remaining 154 articles has been completed. A total of 122 articles were included in the final review of these studies after full-text screening. Figure 3 shows the PRISMA flow chart of the study. Thirty-two articles were excluded on a full-text screen (review articles= 7, articles not specifying drug targets against CoV= 22, articles in a language other than English= 3). Details of studies with significant structural and functional target proteins are summarized in Table 1.

SPIKE PROTIEN:

The spike protein is a clove-shaped, type I-TM protein. The spike protein contains three segments that are the ectodomain (ED) region, the TM region, and the intracellular, short tail-part intracellular domain. The S1 receptor-binding domain (three S1 heads) and the S2 membrane fusion subunit (trimeric stalk) on the C-terminal together comprise the ED. Spike proteins accumulate in trimeric form on the outer surface of the virion, giving it the appearance of a crown called CoV. Spike protein plays an important role in the entry of the virus to the host. Initial interactions between the S1 domain and its host receptor (ACE2 in the case of SARS-CoV and PP 4) In the case of MERS-) and next S2 segment mediated host and viral membrane fusion enables the CoV-genome to reach the host cells and, thus, these proteins are important targets from the drug discovery side. The spike protein also stimulates the host cell's immune response to CoV**.**

S1 DOMAIN:

The core components of the S1 domain are the N-terminal domain (NTD) and the C-terminal domain (CTD). The S1 domain acts on the virus ' surface as a major antigen, and has a receptor-binding domain (RBD). The 18 residues of ACE-2 interact with the SARS-CoV spike protein RBD (contains 14 amino acids), and K341 of ACE-2 and R453 RBD residues plays the most important role for this contact. If point mutated on RBD's D454 or R441, this interferes the binding operation with ACE-2. The S1 domain interacts with host receptors ACE-2 or DPP-4. Anti-ACE-2 antibody blocked the entry and replication of viruses in Vero E6 cells. Another virus binding mechanism to host cell is Using dendritic cell-specific intercellular adhesion molecule 3 non-integrating (DC SIGN receptor) or L SIGN in lymph nodes or in liver. S protein has seven asparagine-linked glycosylation sites (109, 118, 119, 158, 227, 589 and 699), which are crucial to both L-SIGN-based and DC-SIGN-based virus entry into the host.

S2 DOMAIN:

The S2 subunit has two heptad-replicate regions (HR 1 and 2) and a hydrophobic fusion peptide.

Drug design approaches targeting S protein and its interactions:

RBD were targeted in a variety of drug design studies. A peptide sequence with sequence similarity to the RBD of S protein inhibited S1-RBD: ACE-2 interaction and prevented SARS-CoV from reaching Vero cells (IC50 approximately 40 μM). A SARS-CoV RBD-specific antibody (FM6) did not inhibit the incidence of infection. OC43-HR2P, a peptide derived from heptad repeat 2 regions of the S2 domain HCoV-OC43 and tailored Type EK1, shown to inhibit pan-CoV fusion properties. The structure (protein data bank [PDB] ID 5ZUV and 5ZVM) reveals a stable6-helix bundle structure with a long β-HCoV and a long β-HCoV-HR1 domain.

Chloroquine, an antimalarial agent, inhibits SERS-CoV by-endosomal pH and alters the terminal glycosylation of ACE-2, which eventually interferes with the binding of the virus receptor.

Other inhibitors SSAA09E2 block the interaction of S-ACE2, SSAA09E1 inhibits the host protease cathepsin L (which is essential for viral entry), and SSAA09E3 prevents the fusion of the host and viral cell membranes.

Kao et al. identified 18 small molecules targeting the S-ACE-2-mediated entry of the virus into human cells. In 293 T ACE-2-expressing cells, one of these agents (VE607) showed substantial inhibition of SARS-pseudovirusentry. In Vero E6 cells, two other molecules oftetra-O-galloylbeta-D-glucose and luteoline also inhibited SARS-pseudovirus and SARS-CoV infection.In virus-infected Vero E6 cells, the

SARS-CoV S-sequencing siRNA inhibited SARS-CoV replication.

The S230 antibody (origin: memory B-cells of SARS-CoV-infected persons) neutralizes a wide variety of SARS-CoV isolates. S230 antibody The Fab fragment binds to the SARS-CoV complex to neutralize it and its structures are also available (PDB IDs: 6NB6, 6NB7, and 6NB8). The monoclonal antibody, m396, plays a competitive role in RBD binding (PDB ID: 2DD8).

Monoclonal antibody can be generated by immunizing the spike protein of SERS CoV (transgenic mice) or the B-cells of coV-infected individuals. Spike-specific monoclonal antibodies 80R and CR301 block S-ACE-2 interactions and thus neutralize human SARS-CoV (HKu39849 and Tor2) and palm civet (SZ3) infections.

Mice vaccinated with SARS-n DNA showed T-cell immune response (both induction and proliferation), and cytotoxic T-cell response was seen against SARS-DNA-transfected alveolar epithelial cells.

ENVELOPE PROTIENS:

The E protein is the smallest (8.4–12 kDa size) TM structural protein of CoV. Two distinct domains comprise the E protein: the hydrophobic domain and the charged cytoplasmic tail. However, the structure is highly variable among different members of the CoV family

The E protein plays a special role in the morphogenesis of viruses, particularly during assembly and egress. CoVs with no E protein exhibit lower viral titer, immature and inefficient progeny. E-protein oligomerisation leads to the formation of ion channels. However, the significance of these ion channels is still not clear. Many other studies suggest that the E protein works together with others Intracellular proteins and modulates the activity of these proteins. The protein E also acts as a factor in virulence. E protein plays a major role in the assembly and formation of CoV budding. Besides this, E protein was found around the body regions ER and Golgi. Hexamethylene amiloride blocks the activity of this E protein-ion channel in mammalian cells which express SERS-CoV protein envelope.

MEMBRANE PROTIENS:

Maintaining the shape of the viral envelope is the most important function of the M protein, and the M protein performs this function by interacting with other CoV proteins, incorporating the Golgi complex into new virons, and stabilizing the nucleocapsid protein.

The M protein is characterized by three TM domains with C-terminal inside (long) and N-terminal outside (short). Details of the protein structure can be found in UniProt. Through multiple protein-protein interactions, M protein plays a key role in intracellular viral homeostasis. Interaction between M –M, M–S, and M–N proteins plays a special role in viral assembly. M–S interactions are necessary for the interaction of spike protein in the ERGIC complex, also known as the Golgi complex, which is later incorporated into new viral progeny. Interactions M–N are crucial to the stabilization of the RNP complex (nucleocapsid–RNA complex) that forms the viral nucleus. The M protein and the N protein are major viral envelope proteins, defining the viral shape, but they also contribute to the formation and release of virus-like particles.

M protein also contributes to the sensitization of the virus to the host, The SARS-CoV M protein activates the kappa pathway of the nuclear factor and the IFN-beta pathway through a mechanism that is Toll-like to the receptors. A mutated M protein (V-68) once again failed to illicitly respond to an IFN-beta.

Mice vaccinated with SARS-M DNA had T-cell immune response (both induction and proliferation) and SARS-DNA-transfected alveolar epithelial cells had a cytotoxic T-cell response.

NUCLEOCAPSID PROTIENS:

The nucleocapsid protein (N protein)structure is conserved throughout the various members of the CoV family. N-arm, central linker(CL), and C-tail are the three characteristic, intrinsically disordered regions (IDRs) of the nucleocapsid (N) protein. The NTD and CTD are the nucleocapsid protein's principal structural and functional domain. RNA binding is the N protein NTD's most important function whereas dimerisation is the CTD's primary job. Since the CL region is rich in arginine and serine residue, there are also a large number of phosphorylation sites within it. The C-terminal IDRs play an important role in oligomerizing nucleocapside proteins and interactions with N –M proteins.
The most important functions of N protein are the formation and maintenance of the RNP complex. It also regulates viral RNA replication and transcription, and inhibits protein translation through EF1α-mediated action, changes in the metabolism of host cells, the cycle of host cells (N proteins are reported to inhibit CDK4), and apoptosis. The N protein

inhibits cell proliferation in human peripheral blood by inhibiting cytokines.

The NTD includes RNA Binding Sites. The RNA-binding sites on the NTD protein were identified by observing Its interactions with ribonucleoside 5'-mono-phosphates (AMP, UMP, CMP, and GMP) The development of RNA-binding inhibitors using information on the interaction between AMP and UMP binding to the NTDnucleocapside protein. From PDB you can see three-dimensional structure with all complexes, 4LMC,4LM9,4LM7 and 4LI4 respectively. One such molecules is N-(6-oxo-5,6-dihydrophenanthridine-2-yl) (N, N dimethyl amino) (PJ34), designed using the model HCoV-OC43. Binding to NTD by PJ34 affects the binding and replication of CoV genomes.

COV-OC43 N-NTD PJ34 inhibitor crystal structure Complex is given in PDB ID: 4KXJ. Another inhibitor was designed based on interactions between Nucleocapsid protein PJ34 and NTD in which H3 (6-chloro-7-(2-morpholin-4-yl-ethylamino) quinoxaline-5, 8-dione) is present, also inhibiting binding RNA. The importance of NTD in RNA binding is emphasized in this.

Some of the herbal products, like catechin gallate and gallocatechin gallate (both polyphenolic compounds) have shown an inhibitory action against SARS-CoV

PROTEASES:

The genome SERS-CoV encodes a series of proteins. The replicase gene which is a major component of the encoded CoV genome in the form of two large PPs (PP1a and PP1ab) for 16 NSPs. Two types of cysteine proteases act to release the NSPs on those PPs. The C-terminal end of these PPs is cleaved by chymotrypsin-like cysteine protease (main protease [Mpro] or 3C-like protease [3CLpro]) and the N-terminal end is processed by Mpro (also known as papain-like protease [PLpro]). The first three PPs cleavage sites are cut by PLpro while the remaining 11 sites are cleaved by CLpro, resulting in the release of 16 NSPs.

3C LIKE PROTEASE:

The 3CLpro is present in homodimer form and has on active site cys-his dyad which shows protease activity. If mutated on the positions Ser139 and phe140, the dimerisation of 3CLPro (PDB ID: 3F9 G) is abolished. This protease can split 11 sites in the PP1a and PP1ab position p1, and can produce a mature protein that anchors the replication / transcription complex and also releases mature NSPs

Another important inhibitor of CLPro is N-(benzo[1,2,3]triazol-1-yl)-N-(benzyl) acetamido) phenyl) carboxamides. CLPro inhibitor structure is reported with ML188 (IC50 1.5 μM) (CID: 46897844,PDB ID: 3V3 M). Another structure is reported to have CLPro inhibitor ML300 (PDB ID: 4MDS, IC50: 6.2 μM). Some metal-conjugated and peptidomimetic compounds showed inhibitory activity against 3CLpro. Some of the small molecules also act as an inhibitor that is analogous to arylboronic acids, quinolinecarboxylate derivatives, thiophenecarboxylate, and ketoglutamine-substituted phthalhydrazide]. It's also reported that some flavonoids inhibit Mpro. GC376 also has inhibitory protease activity. Also reported is an Mpro crystal structure with smallMolecule inhibitor N3 (PDB ID: 2AMQ). Mpro is also inhibited by lopinavir and ritonavir, which are the HIV protease inhibitors. In silico studies, valrubicin icatibant, bepotastine, epirubicin, epoprostenolol, vapreotide, aprepitant, caspofungin, and perphenazine also bind to the CoV-binding site for lopinavir / ritonavir among commercially available drugscolistin.

Hemagglutinin esterase

This HE enzyme is present in the CoV envelope, more specifically among beta-coronaviridiae. The HE is a marker of evolution of the CoV and influenza viruses. HE mediates reversible attachment to O-acetylated-sialic-acids by acting as both lectins and receptor-destructive enzymes. Interactions between HE in complex and sialic acid can be visualized in PDB ID: 3CL5.

NTPase/helicase:

NTPase / helicase plays a key role in the central dogma of the virus. The enzyme SARS-CoV helicase is a member of the SF1. This enzyme prefers ATP, dATP, and dCTP as substrates; it also hydrolyzes all NTPs. Toxicity issues are major barriers to the development of helicase inhibitors, and the lack of specificity of inhibitors can cause serious toxicity. However, despite theoretical limitations, helicase is increasingly recognized as a druggable target for different disease conditions.

Papain-like protease:

PLpro generates three NSPs (NSP 1, 2 and 3) in the N-terminal region of PP. PLpro has a catalytic core domain containing 316 amino acids, which is responsible for the cleavage of replicate substrates, and a consensus sequence of LXGG was required for cleavage. Higher doses of zinc and zinc conjugates have been shown to inhibit both types of SARS protease (CLpro and PLpro). Benzodioxole may inhibit

the enzyme of PLpro. The crystal structure of the interaction is shown in PDB ID: 4OVZ,4OWZ. A further optimized new lead (6577871) was identified in the Silico approach and compounds 15h (S configuration, enzyme IC50=0.56μM, antiviral EC50=9.1 μM) and 15 g (R configuration, enzyme IC50=0.32 μM; antiviral EC50=9.1 μM) were found to be the most important inhibitors. The crystallized structural details of these interactions can be viewed in the PDB (PDB ID: 2FE8 and 3E9S) database. Many of the protease inhibitors are used in the treatment of COVID-19, e.g. lopinavir–ritonavir combinations.

CLINICAL TRAIL UPDATE:

To date, a total of 233 trials have been registered in the Chinese Clinical Trial Registry (dated 24 February 2020, keywords 2019-nCov and COVID-19). High doses of vitamin C, favipiravir, adalimumab, dihydro-artemisinin piperaquine, leflunomide, dipyridamole, chloroquine or hydroxychloroquine are among the pharmacotherapeutic agents evaluated. Suramine sodium, lopinavir / ritonavirandarbidol (umifenovir) tablets and IFN-alpha 2b tablets. Other Important agents to be evaluated are Huo-Shen particles, Xiyanping injection, Shen-Fu injection, etc., many of which come from traditional Chinese medicines. The use of stem cells is also often evaluated.

V. CONCLUSION

Drug discovery against CoV is a challenging task due to frequent recombination events. Another important aspect is the development of a vaccine.

More structural biology details and details of the life cycle of the CoV are needed, which can accelerate the development of the drug / vaccine process against CoV. Again, as a preventive measure, strict vigilance of viral changes in different hosts is important in predicting an event.

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Figure 3: Flowchart

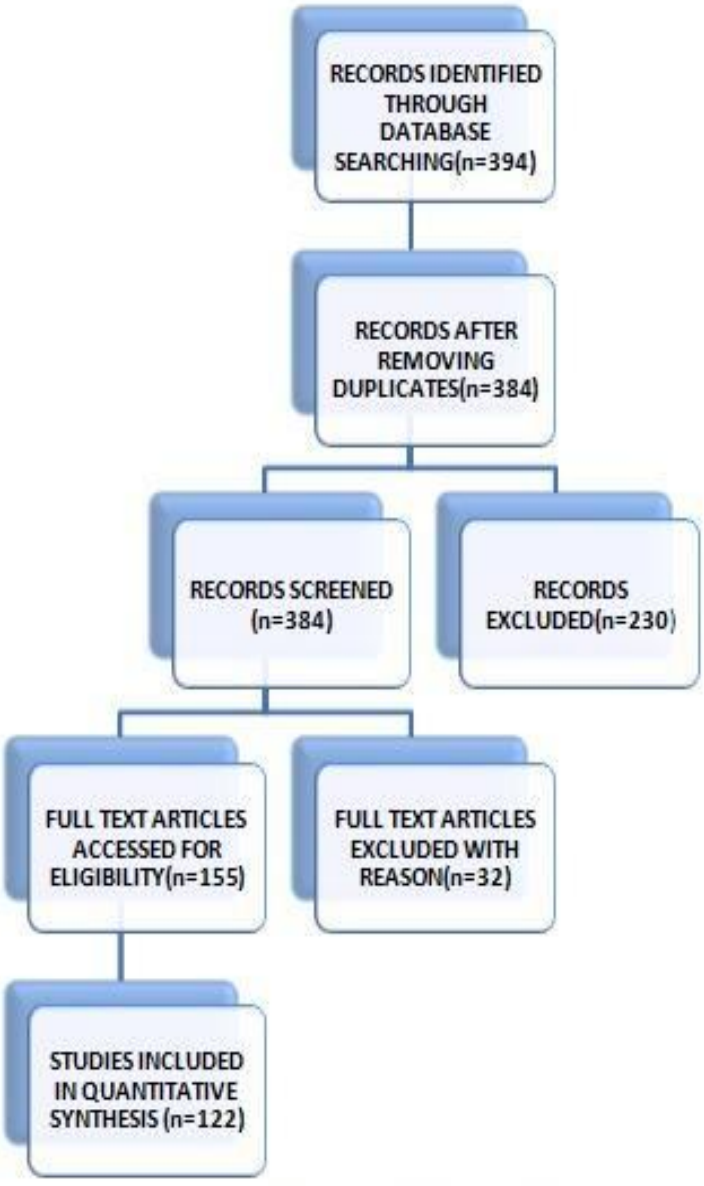

Table 1: Details of studies representing protein database structures of major targets in coronavirus and their structures

PDB ID	Details	Inhibitor	IC_{50}	Reference
		N protein		
4KXJ	Interaction between PJ34 and NTD of N protein of HCoV-OC43	PJ34	-	[26]
3V3P	Structure not released			[30]
4LM7	Interactions of NTD of N protein of HCoV-OC43 with UMP	-		[26]
4LI4	Interactions of NTD of N protein of HCoV-OC43 with AMP	-		[26]
		Protease		
4TWY	3CLPro of SARS-CoV with an inhibitor	3BL		[27]
4TWW	3CLPro of SARS-CoV with an inhibitor	41	63 μM	[27]
4WY3	3CLPro of SARS-CoV with an inhibitor	3X5	240 μM	[27]
4OVZ	CoV PLPro complexed with inhibitor	P85	490 nM	[31]
3MJ5	SARS-CoV PL^{Pro} complexed with inhibitor	GRM	320 nM	[32]
2FE8	SARS-CoV PL^{Pro}	-	-	[33]
1UK4	SARS-CoV $3CL^{Pro}$ and its interactions with an inhibitor	Substrate analog hexapeptidyl CMK inhibitor	IC_{50} ca. 2 mM	[34]
1UJ1, 1UK3, 1UK2	SARS-CoV M-pro, apo-enzyme at different pH	-	-	[34]
3VB6	SARS-CoV 3CLPro in complex with C6Z	C6Z	39 μM	[35]
3VB5	SARS-CoV 3CLPro with C4Z	C4Z	1.3-4.6 μM	[35]
3TLO	HCoV-NL63 3CLPro	-	-	[36,37]
6LU7	Main protease of 2019-nCoV and its complex with N3 (inhibitor)	-	-	[38]
		Spike protein		
5ZUV	HR1 motif of HCoV-229E in complex with EK1	Modified OC43-HR2P peptide (EK1)	0.19-0.62 μM	[39]
5ZVM	EK1 in complex with SARS HR1 motif			[39]
5X4S	NTD of SARS-CoV S protein			[40]
5WRG	SARS-CoV S protein			[41]
6Q05	MERS-CoV S structure in complex with Sialyl-Lewis			[42]
6ACG	SARS-CoV S protein: ACE-2 (conformation 1) complex			[43]
6ACK	SARS-CoV S protein: ACE-2 (conformation 3) complex			[43]
3SCI	RBD of S protein interaction with ACE-2			[44] to be published

NTD=N-terminal domain, CoV=Coronovirus, 3CLPro=3C-like protease, PL^{pro}=Papain-like protease, MERS=Middle East respiratory syndrome, SARS=Severe acute respiratory syndrome, ACE-2=Angiotensin converting enzyme-2, RBD=Receptor-binding domain, nCoV=Novel coronavirus, S protein=Spike protein