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REVIEW ARTICLE

An overview of COVID-19 with an emphasis on computational approach for its preventive intervention

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Abstract

SARS-CoV-2, a novel *Betacoronavirus*, has attracted global attention because of its extremely high infection rate and large number of human deaths. It possesses a positive-sense, single-stranded RNA of ~ 30 kb nucleotides as its genetic material. It is responsible for COVID-19 which has been declared a pandemic by WHO. Having reported for the first time in Wuhan, China, the virus infected over 21.48 million people and caused over 0.77 million deaths till mid-august 2020. SARS-CoV-2 contains the spike protein site that gets activated by an enzyme furin which is found in the lung, liver, and small intestine of humans. It shows the potentiality of virus for attacking multiple organs and their failures. Due to the absence of vaccines, the cure is restricted to supportive care including repurposed drugs. In silico approaches may offer an alternative screening to optimize hits to lead stages. It can provide important related to drug resistance, their lineages and evolution. This approach may also help to find an effective vaccine against COVID-19. This review focuses on the in silico aspects of genomics, proteomics, pathogenesis, phylogenetic analysis and viral receptor binding analysis in *Betacoronavirus*.

Keywords SARS-CoV-2 · *Betacoronavirus* · COVID-19 · In silico · Vaccine

Introduction

COVID-19 pandemic takes us back in the history reminding to 1918 influenza pandemic caused by the H1N1 virus which infected about 500 million and took a death toll of about 50 million people. Viral pandemic has a great impact on human beings from infection, morbidity, mortality and fear of economic instability. Some major outbreak of the viral disease since the early twentieth century is depicted in Table1. The Coronaviruses consist of club-like projections that cause colds and acute upper respiratory distress, also in some cases mild pneumonia and acute gastroenteritis. They inflict various disorders in a wide range of birds and mammals and are transmissible in humans also. In December 2019, people infected from this virus reported having symptoms similar to that of pneumonia (Gupta et al. 2020). Later on, it was discovered as novel coronavirus and renamed as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the World Health Organisation. This novel *Betacoronavirus* has brought the entire planet at the knee because of its tremendous high infection rate resulting in large number of deaths. It belongs to the family of *coronaviridae* possessing a positive-sense, single-stranded RNA of ~ 30 kb nucleotides as its genetic material (Shereen et al. 2020). It is responsible for spreading coronavirus disease 2019 (COVID-19) which has been declared a pandemic by WHO. Having originated in Wuhan, China, this virus made almost all the world victim infecting more than 21.48 million people and causing more than 0.77 million deaths as of 16 August 2020 (JHU 2020), and these numbers are increasing with each passing day (Liu et al. 2020). Since these numbers are progressing at a great pace, there is an urgent need to understand the exact mechanisms related to the pathogenicity. It will assist in making an efficient remedy for early-stage prevention and regulation of the outbreak.

SARS-CoV-2 is an enveloped virus that differs from other members of the virus family in that it contains a spike protein site that gets activated by furin which is an enzyme of the infected host cell (Singhal 2020). Many human tissues including lungs, liver and small intestines contain receptors like furin. This shows the potentiality of coronaviruses for

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Table 1 Major outbreak of viral diseases since early twentieth century

Year	Disease	Infection	Mortality (estimated death)	Country badly affected	References
1918–19	Influenza (H1N1 virus) (Spanish flu; misnomer)	500 million people	50 million worldwide	USA > half million people killed	CDC (2018)
1940s and 1950s	Polio	35,000 people each year	2720 deaths United States	United States and Canada	CDC (2019a, b, c)
1957s–1958s	Asian Flu	–	1.1 million worldwide	East Asia	CDC (2019a, b, c)
1968s	Influenza	–	1 million worldwide	United States	CDC (2019a, b, c)
1960s	Marburg hemorrhagic fever	31	7	Germany and in Belgrade, Yugoslavia (now Serbia)	CDC (2014)
2014–2016	Ebola hemorrhagic disease	28,616	11,310 worldwide	Liberia, Guinea, Sierra Leone (West Africa)	WHO (2016)
1980s and 1990s	AIDS		770,000 (2018) worldwide	Africa	Wikipedia. Epidemiology of HIV/AIDS (2020a)
1996	Hepatitis	> 391 million (2017)	65,400 direct (2015), > 750,000 (total)	Worldwide	Wikipedia. Hepatitis (2020b)
2002	West Nile Fever	3389 cases	704 persons	USA	CDC (2002)
2003	SARS	8096	774 worldwide	Worldwide	WHO (2004)
2009	Influenza	60.8 million cases	151,700–575,400 worldwide	United States	CDC (2019a, b, c)
2019	COVID-19	21 million on 16 August 2020	0.77 million on 16 August 2020	USA	John Hopkins University. (JHU) (2020)

attacking multiple human organs resulting in their failure. Like a typical influenza virus, the new coronavirus uses its spike proteins as a key to enter into a host cell, where its internal machinery takes over for repurposing and building the new components of viruses. When an infected person coughs or sneezes, the droplets carrying the virus may spread to others through mouth, nose and in turn affects the lungs and other organs. Thus, the mode of transmission is the physical contact with infected patients, infected intermediate surfaces or objects used by infected persons (Dhama et al. 2020). The spread of this deadly virus can only be regulated by imposing curfew, lockdown, quarantine, isolation and social distancing along with enhancement of immunity following Ayurveda's prescription and proscription. Presently, due to unavailability of licensed vaccines or drugs, the cure is restricted to supportive care with few repurposed drugs. Thus, to cope with this unprecedented situation, the in silico approach may offer an alternative screening to optimize hits to the lead stage. The in silico method recognize the viral proteins that interacts with the human host system helping in drug targeting. The comparative analysis of coronavirus with other group of *coronaviridae* members leads to the finding of the major characteristics that further determine the unique properties of viral species or isolates to contribution in pathogenicity (Dhama et al. 2020). This approach can also help in finding an effective drug or vaccine against COVID-19. In this review, the in silico aspects to understand and prevent SARS-CoV-2 have been discussed. We have further provided the information related to in silico insights to genomics, proteomics, pathogenesis, phylogenetic analysis and viral receptor binding analysis in *Betacoronavirus*.

Etiology and transmission of SARS-CoV-2

Coronaviruses are positive-sense, single-stranded RNA having crown-like appearance because of the ubiquity of spike proteins on their surfaces. It belongs to the family *coronaviridae* that is classified into four genera viz. gamma, delta, alpha and beta coronaviruses. The beta coronaviruses are further sub-divided into five lineages. From the genome recombination, alpha-CoVs and beta-CoVs are found to be the gene sources of bats and rabbits that infect humans. On the other hand, delta-CoVs and gamma-CoVs seem to originate from the avian species (Kumar 2020). Therefore, a substantial group of viruses can infect the respiratory tract and hepatic cells in several organisms, including rodents, cats, bats, and cattle. In the present scenario, few CoVs are potentially becoming capable of heading towards infecting

humans (Lahiri et al. 2020). This spread from animals to humans started way back in the 1960s and one such member of the coronavirus family is identified recently. An estimation shows that approximately 2% of the general population is the potential carrier of CoVs and these viruses are reported to cause about 10% of the acute respiratory infection. Some human CoVs strains, for example, HcoVs-HKU1, HcoVs-229E, HcoVs-O43 also HcoVs-NL63 can cause the common cold, mild upper respiratory tract infection and in elderly, they can cause lower respiratory tract infection. Besides SARS-CoV-2, other Human CoVs i.e. SARS-CoV-2, MERS-CoVS can cause epidemic including various clinical stern featuring respiratory or extra respiratory instances having a mortality rate of 35% mutually (Cascella et al. 2020). The SARS-CoV-2 belongs to the category of beta coronaviruses having more than 79% genomic similarity with SARS-CoV (Wang et al. 2020) and 50% similarity with MERS-CoV. SARS-CoV-2 is elliptical and pleomorphic with the diameter ranging from 60 to 140 nm. As shown in Fig. 1, the SARS-CoV-2 consists of the following components: spike glycoprotein (S), membrane protein (M), an envelope protein (E), nucleocapsid protein (N) and ssRNA.

The SARS-CoV-2 infection which is a contagious viral infection primarily targets the human throat and lungs. The mode of transmission is through close contact with the infected person's coughing and sneezing droplets. In other words, this virus spread through tiny airborne droplets. As a result, it causes cellular damage through the replication in the ciliated epithelium. It is reported by some scientists that the coronavirus uses angiotensin-converting enzyme-2, a membrane receptor for entering into the human cell (Wang et al. 2020). The mode of transmission of SARS-CoV-2 is shown in Fig. 2.

Replications and pathogenesis

Inside the coronavirus, genetic material contains the information to make more copies of it. Their protein shell provides a hard-protective enclosure for the genetic material as the virus travels within the person it infects. The CoVs genome is positive-sense, single-stranded having 5′-cap structure and polyA tail at 3-prime. According to some researchers, angiotensin-converting enzyme-2 (ACE2) is present in the human's lower respiratory tract that behaves as a cell receptor for SARS-CoVs and regulates its transmission to the humans or cross-species. Recently, researches confirmed that SARS-CoV-2 also uses the same machinery to enter into the human cell. The viral spike proteins (S) get attached to the ACE2 cell surface receptor (Guo et al. 2020). Therefore, S1 protein can regulate the host–pathogen range as well as cellular tropisms with the RBD domain, whereas S2 protein arbitrates the fusion of pathogen-cell membrane via two club domains, i.e., heptad repeats 1, and heptad repeats 2.

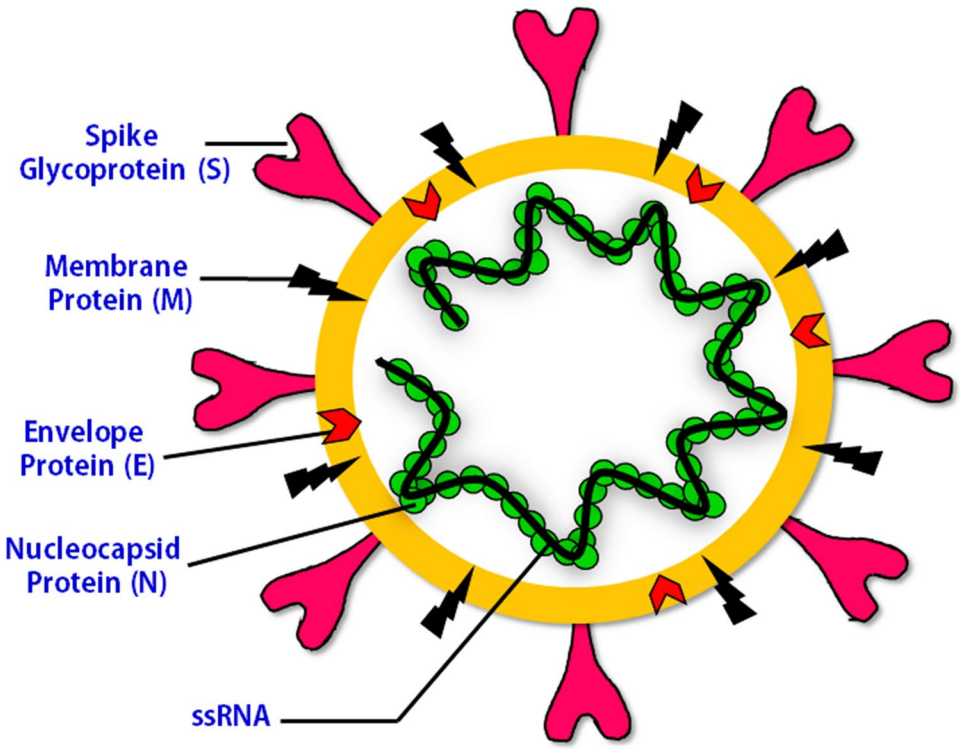

Fig. 1 Diagrammatic illustration of structure of SARS-CoV-2

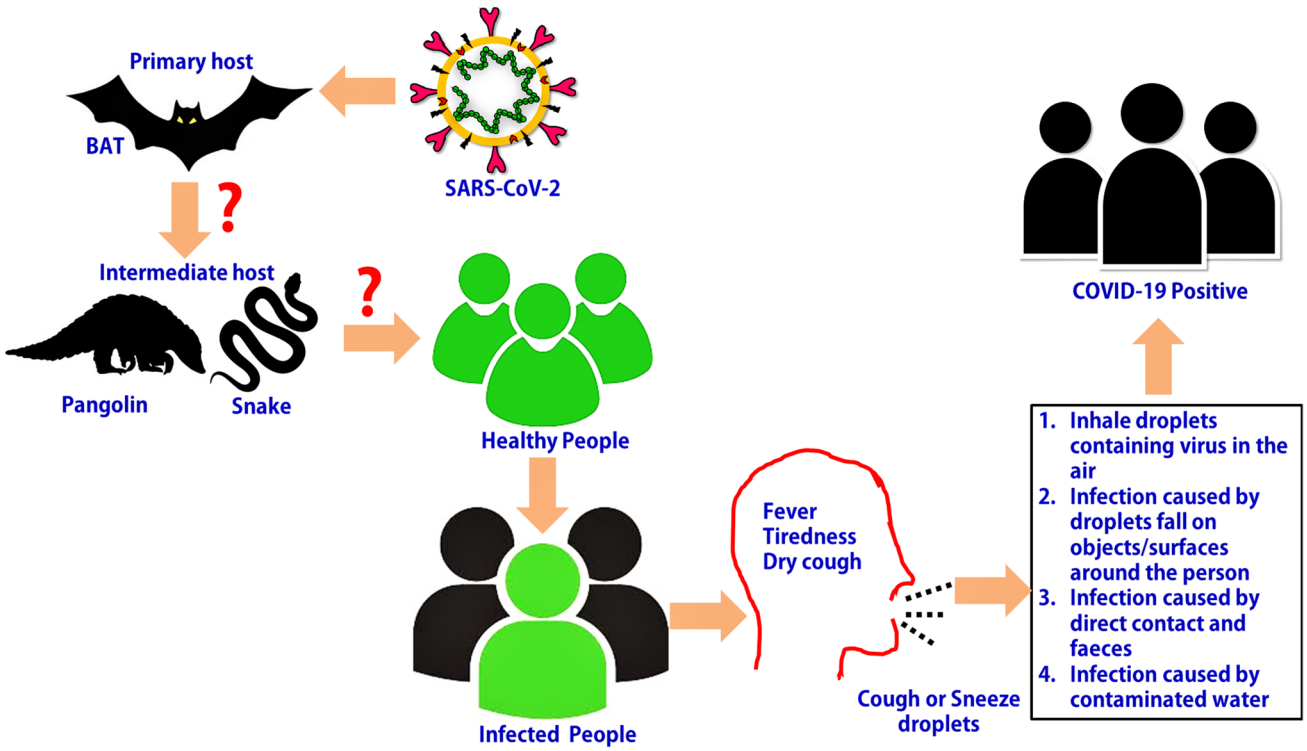

Fig. 2 Diagrammatic depiction of mode of infection and transmission of SARS-CoV-2

After the cell membrane fusion, the viral RNA gets dispensed into the host cytoplasm, the viral genomic RNA directly used as a template to translate polyproteins 1a and 1b. The PP1a and PP1ab proteins cipher the non-structural proteins to form the transcription–replication complex inside the double membrane sac. RNA-dependent RNA-polymerase acts as a critical component (nsp12) that catalyzes the viral RNA synthesis and also plays a crucial role in the replication–transcription machinery of COVID-19 with nsp7 and nsp8 as cofactors. Likewise, transcription–replication complexes can synthesize a sub-genomic RNA group that encodes the structural and accessory proteins (Guo et al. 2020). Subsequently, a sub-genomic nested set of RNA is synthesized via the replication–transcription complex as discontinuous transcription. These sequences commonly possess 5′-guide and 3′-terminal sequences. The termination and acquisition of subsequent transcription of guide RNA may occur at the site of transcription regulatory sequences placed between open reading frames (Scotti and Scotti 2018). The sub-genomic RNA −ve strand aided as the template for sub-genomic messenger RNA production. The viral genomes and sub-genomes of coronaviruses consist of at least six open reading frames. There is −ve frameshift between open reading frame1a and open reading frame 1b causing the polypeptides 1a and polypeptides1 ab production. These polypeptides are processed via viral encoded chymotrypsin-like protease enzyme and the main proteases enzymes into 16 nsps. Likewise, other open reading frames near 3′-strand encodes the main structural proteins of SARS-CoV-2, i.e., spike, envelop, nucleocapsid, and membrane protein. Also, different coronaviruses encode the particular structural and accessory proteins, i.e., 3a/b, 4a/b, and hemagglutinin-esterase proteins (Scotti and Scotti 2018). The structural and accessory proteins may help to arbitrate the endoplasmic reticulum and Golgi body. Besides this, the newly developed viral RNA, along with its accessory proteins, assembles and forms a bud of the viral particle. Finally, the sac containing the viral particles gets fused along the cell plasma membrane to discharge the viruses (Guo et al. 2020). The pictorial representation of the viral replication mechanism is shown in Fig. 3.

The critical step shows the viral spike protein binding with the ACE2 receptor to enter into the human cell. Therefore, the viral–host receptor binding affinity is accelerated via different approaches. On the one hand, systematic studies of *Betacoronavirus* receptors demonstrate that human cell expresses only the ACE2 receptor, still it does not show aminopeptidase N or dipeptidase-4 that enhances the entry of SARS-CoV-2. While on the other hand, another detection procedure may prove that spike protein binding efficacy with the ACE2 receptor is 10–20-fold higher than SARS-CoVs through SARS-CoV-2 cryo-EM structure (Shereen et al. 2020). The available data suggest that the mortality rate of

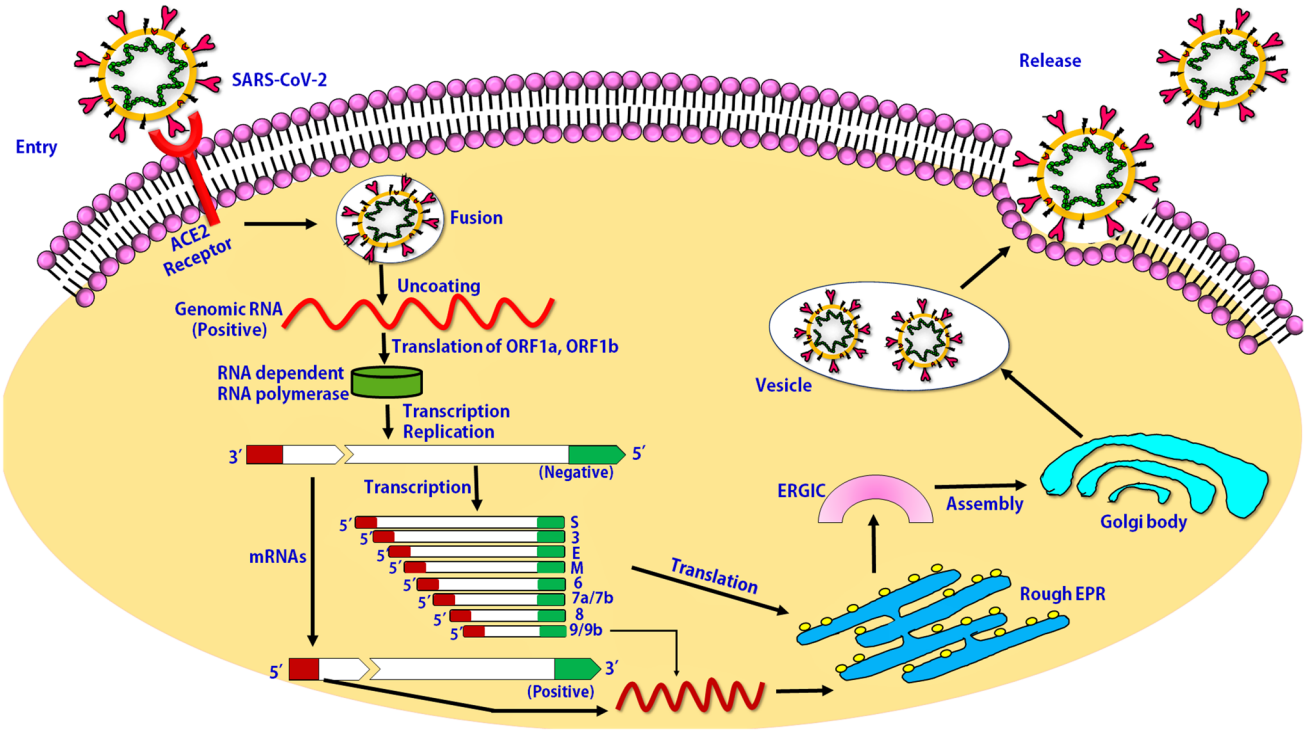

Fig. 3 Pictorial representation of viral–host interaction and replication of the virus SARS-CoV-2

SARS-CoVs (9.6%) and MARS-CoVs (~35%), respectively, were higher than that of SARS-CoV-2 (3.4%) (2).

Clinical characteristics/features

SARS-CoV-2 infects many people in different ways. Most of the time, the diseased patients may develop asymptotic to mild symptoms. Its common clinical characteristics are associated with fever, sore throat, breathlessness, and cough. Hence, it has similar characteristic features to other respiratory infections. Most of the time younger and adult patients may develop asymptotic symptoms; likewise, few patients may also develop critical and acute lung distress syndrome. At the end of the first week, pneumonia, lung failure, and death progress are commonly observed in the corona-infected patients (Guo et al. 2020). These symptoms progression are associated with the acute inflammatory cytokines that contain IL2, IP10, IL10, IL7, MIP1A, and tumour necrosis factor-alpha. However, the signs of dyspnea progression median time appear in 5 days. In contrast, severe lungs distress syndrome progression median time has been observed in 8 days. However, the associated complexities are chronic lung injury, acute lung distress syndrome, and kidney failure. The patients start recuperating within 7–14 days, and the average time for staying in hospitals may be ~ 10 days. Likewise, the fatality rate in elders ranges from 4 to 11%, and the approximate fatality rate ~ 3% (Guo et al. 2020).

Diagnostic criteria

The molecular technique used to detect COVID-19 is a real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab or sputum sample. In RT-PCR, the RNA template is first converted into a complementary DNA (cDNA) using a reverse transcriptase enzyme. The cDNA is then used as a template for exponential amplification using PCR. This is known as 'reverse transcription'. Here, the DNA copied or amplified is a key part of the real-time RT-PCR process for detecting viruses. Amplification of a specific part of the transcribed viral DNA gives hundreds of thousands of copies. Amplification is important so that instead of trying to spot a minuscule amount of the virus among millions of strands of genetic information, scientists have enough quantity of the target sections of viral DNA to accurately confirm that the presence of virus. The advantages of this test are that it is most specific, sensitive and reproducible and it is not influenced by non-specific amplification. However, the disadvantages are that this is time-consuming process and needs great precautions since the person involved in testing can get infected. Besides, it requires high technical skill and support. Keeping in view,

the global emergency situation rapid test kit is being used for the detection of COVID-19.

Antibody based

The antibody test is another standard rapid detection method marketed for COVID-19, a test that detects the presence of antibodies in the infected patients' blood. Antibodies are produced over days to weeks after infection with the virus (Zhao et al. 2018). The strength of antibody response depends on several factors, including age, nutritional status, severity of the disease, and certain medications or infections like HIV that suppress the immune system (WHO).

Antigen based

Nowadays, antigen testing is also in trends to detect the presence of SARS-CoV-2 infection. Therefore, it detects the presence of viral proteins (antigens) expression in a sample from the patient's respiratory tract. If the target antigen is presented into sufficient concentrations in the sample, in that case, it will bind to specific antibodies fixed to a paper strip and generate a visually detectable signal, typically within 30 min. The antigen(s) expression is detected only when the virus is actively replicating; therefore, such tests are best used to identify acute or early infection (WHO).

Genomic and proteomic characterization of SARS-CoV-2

The infection rate of SARS-CoV-2 is increasing at an incredible pace, and still, there is no availability of licensed drugs or vaccines. In this grave situation, when the whole world is fighting against this deadly virus, there is an emergent need for finding a suitable drug or vaccine that could assist in the treatment against COVID-19. As the in vitro and in vivo approach is time consuming, the best strategy is available in the in silico approach. Theoretical methods implementing the in silico method will assist in the process of discovering drugs and will be advantageous in selecting potential compound leads in a short period. The in silico approach will also be efficient and, at the same time, cost-effective also as compared to the traditional experimental testing (Mousavizadeha and Ghasemi 2020). There are innumerable fields where the in silico or computational approach is employed to analyze a vast amount of biological data available in various databases. These include genomics, proteomics, transcriptomics, metabolomics, metagenomics, etc. The SARS-CoV-2 sequenced genome has been deposited in the NCBI repositories from different laboratories throughout the world. The SARS-CoV-2 has +ve sense, single-stranded RNA consisting 29.811 bp long nucleotides, i.e., adenosine (29.86%), cytosine (18.39%), guanines (19.63%), and thymine (32.12%). In open reading frames, five mutations have been identified in ORF1a T8782C (silent mutation), T9561C (non-silent mutation); likewise, in open reading frame 1b C15607T (silent mutation), ORF8b C28144T (non-silent mutation) and nucleocapsid codon T29095C (silent mutation), respectively (Lu et al. 2020). Genomics deals with the study of whole genomes of organisms and implements the in silico approach for sequencing, assembling, and analyzing the structure and function of genomes. Today, next-generation sequencing technology leads to a striking improvement in the speed, capacity, and affordability of genome sequencing (Liu et al. 2020). Sample sequencing of COVID-19 infected patients already done using this technology. Phylogenetic analysis reveals the evolutionary relationship among different coronaviruses that reveals the samples of SARS-CoV-2 is similar to SARS-CoV. Both the samples were similar to that of bats and hence anticipated the evolutionary relationship of the coronavirus (Dagur and Dhakar 2020). Also, another application of in silico genomics characterization is gene co-expression analysis between SARS-CoVS and SARS-CoV-2. Likewise, network analysis also paves the way for the study of gene co-expression and exploring associated genes potentiality in treating a disease. On the one hand, with the help of network analysis, we can identify the targeted genes associated with familiar drugs and their role in the treatment of COVID-19. Hence, using the in silico approach in genomics will help find of a suitable cure for the treatment of COVID-19. Many types of protein sequences identified in the viral genome encoded several structural and non-structural proteins. The structural protein in SARS-CoV-2 includes RNA-dependent RNA polymerases, i.e., RdRp, viral spike proteins, envelope, membrane, nucleocapsid protein and 5′ and 3′ untranslated regions (Lu et al. 2020). Likewise, viral non-structural proteins such as open reading frames (ORF 3a, ORF 7a, and ORF8) act as an accessory protein playing a role in the pathogenesis of viruses (Lu et al. 2020). Therefore, with the help of SARS-CoV-2 spike protein sequences, the 3D form of structure has been predicted into two open and closed conformations through cryo-electron microscopy. These predicted structures deposited in the protein data bank repositories have PDB ID 6VXX and 6VYB, respectively (Liu and Wang 2020). Therefore, the in silico proteomics characterization deals with the analysis of the structure and function of proteins. Proteomics also finds an application in drug discovery as the majority of small molecules drugs act on protein targets. The drug targeting approach initializes by selecting a protein target based on its validated role in the relevant disease and the hits identified through virtual screening, high throughput analysis using large databases libraries of small molecules. After in silico optimization, the testing will be done for the in vivo efficacy in their respective disease model. Proteomics has also been implemented successfully in biomarker discovery, lead optimization, target identification, and validation. In the case of SARS-CoV-2, also

researchers have implemented the in silco approach to identify the drug targets using molecular docking.

In silico identification of drug targets and potential drug repurposing

The in silico approach for predicting the bioactive compounds targets will save cost and time in the research and development of a drug (Dagur and Dhakar 2020). Drug repurposing or drug repositioning is a technique for generating an additional value of an already existing drugs by targeting a different disease rather than the disease for which it was developed initially (Lu et al. 2020). Drug repurposing has the capability of yielding new therapies at a faster rate than that of the discovery of a novel drug. This yielding of new treatments can be done even more quickly when the drug is already approved, and the data related to post-marketing safety surveillance are available (Shey et al. 2019). In this framework, the testing of various repurposed drugs is already done against COVID-19, such as for phase-3, Remdesivir is being tested worldwide, Chloroquine phosphate for phase-4 and Carrimycin also for phase-4 in China (Liu et al. 2020). In silico methods provide a way for rapidly and methodically yielding additional repurposing candidates (Joshi et al. 2020). So, for a case when we know the drug targets which is associated with the disease of interest and when we have the availability of the protein structures or that of close homologs, we can use structural bioinformatics for virtual screening (molecular docking) an existing drugs library against these known targets (Joshi et al. 2020). A study done by Wu et al. relied on the virtual screening approach, using the predicted structures of all SARS-CoV-2 proteins based on their homology with the protein structures of other known coronaviruses. This method is aided in identifying several compounds having a potent anti-viral activity (Sun et al. 2018). Another in silico approach for the drug repurposing is the network bioinformatics approach. It is different from a structure-based method that relies on various known targets (Sun et al. 2018). In contrast, in the network bioinformatics approach, prioritizing of the potential drug targets and the existing drugs is done in return to the threats of this global infectious disease. Here a few potential repurposed drugs are given in Table 2.

In silico vaccine development

The computational approaches are efficient and time-saving process. It can help in hastening the candidate peptides finding and designing for the vaccine development. The use of multi-epitope vaccines is currently known to be an effective immunizing strategy against the viruses that can breed more extensive defence immunity (Behbahani 2020). After the WHO announcement for emergent situations on COVID-19 infection, the health scientists urged to find an efficient therapy mainly focusing on drug candidate identification. Therefore, a lucrative and less tedious process is employed that is essential to be implemented for predicting active antigenic epitopes to develop multi-epitope vaccines. The schematic diagram of in silico vaccine development shown in Fig. 4

In comparison to classical antigen-based vaccines, multi-epitope vaccine development has a more distinctive approach. The basic concept for in silico identification of the viral genome is to find an immunological epitope that can lead to the elicited immune response without any reversal of viral pathogenesis. With the assistance of immunoinformatics approach, the analysis of the entire spectrum antigen is easily achievable (Dhama et al. 2020). Likewise, B and CTL cell antigen estimation through the different methods of immunoinformatics are considered as a vital tool for multi-epitope vaccine development. Because of the high pathogenicity of COVID-19, the vaccine development against viral pathogens is challenging. These restraints could be reduced by applying the in silico method. The advancement of several bioinformatics tools also helps in hastening the advancement of multi-epitope vaccine design. Recently, many researchers are working to design in silico-based novel multi-epitope recombinant vaccine that depends on the SARS-CoV-2 surface glycoproteins. This development could help with the growth of efficient immunization against several pathogen serotypes, while reduced immunogenicity provides significant drawbacks in the event of vaccines (Han and Kral 2020). Likewise, in Behbahani (2020), they have mentioned the unique multi-step in silico approach to design a multi-epitope recombinant vaccine against COVID-19. Their respective potential vaccine contained 17 epitopes with AAY, KK linkers and L7/L12 50s ribosomal protein as an adjuvant. It is reported that the proposed multi-epitope vaccine having high aliphatic index, low instability, negative gravy indices, relatively stable and potentially antigenic. Therefore, with the assistance of a computational approach, we can evolve a highly stable and potential antigen against SARS-CoV-2 infection. In several other countries, they were collaboratively working on vaccine trials on humans. Early results of vaccine trials have consolidated, although as far as data were analyzed and full clinical experimentations were done, experts cannot be sure that any of the remedies are potential or safe. Therefore, experts said that the world would be capable of defeating COVID-19 when a vaccine is ready to distribute widely.

Table 2 List of potential repurposed drugs against SARS-CoV-2

Drug name	Accession number	Type	Group	Category	Target(s)	Method	References
Nelfinavir	DB00220	Small molecule	Approved	Anti-viral	HIV-1 protease	Virtual screening	Liu et al. (2020)
Valrubicin	DB00385	Small molecule	Approved	Enzyme inhibitor	1. DNA 2. DNA topoisomerase 2-alpha	Virtual screening	Jin et al. (2020)
Rupintrivir	DB05102	Small molecule	Investigational	Anti-viral	Genome polyprotein	Virtual screening	Liu et al. (2020)
Lopinavir	DB01601	Small molecule	Approved	Anti-viral	HIV-1 protease	Virtual screening	Liu et al. (2020)
Remdesivir	DB14761	Small molecule	Investigational	Anti-viral	1. Replicase polyprotein 1ab 2. RNA-directed RNA polymerase L	Virtual screening	Liu et al. (2020)
Ebselen	DB12610	Small molecule	Investigational	Anti-rheumatic	Bifunctional epoxide hydrolase 2	Virtual screening	Contini (2020)
Indinavir	DB00224	Small molecule	Approved	Anti-viral	HIV-1 protease	Virtual screening	Wang et al. (2020)
Hydroxychloroquine	DB01611	Small molecule	Approved	Anti-malarial	1. DNA 2. Toll-like receptor 7 3. Toll-like receptor 9 4. Angiotensin-converting enzyme-2	Virtual screening	Beck et al. (2020)
Streptomycin	DB01082	Small molecule	Approved	Anti-infective	1. 30S ribosomal protein S12 2. 16S ribosomal RNA 3. Protein-arginine deiminase type-4	Virtual screening	Beck et al. (2020)
Ritonavir	DB00503	Small molecule	Approved	Antiviral	1. HIV-1 protease 2. Nuclear receptor subfamily 1 group I member 2	Virtual screening	Elfiky and Ibrahim (2019)
Saquinavir	DB01232	Small molecule	Approved, investigational	Anti-viral	HIV-1 protease	Virtual screening	Beck et al. (2020)
Grazoprevir	DB11575	Small molecule	Approved	Anti-viral	NS3/4A protein	Virtual screening	Arya et al. (2020)

Table 2 (continued)

Drug name	Accession number	Type	Group	Category	Target(s)	Method	References
Chloroquine	DB00608	Small molecule	Approved, investigational	Anti-malarial	1. Glutathione *S*-transferase A2 2. Tumor necrosis factor 3. Toll-like receptor 9 4. Glutathione *S*-transferase 5. High mobility group protein B1 6. Glutathione *S*-transferase Mu 1 7. Angiotensin-converting enzyme-2	Virtual screening	Smith and Smith (2020)
Hypericin	DB13014	Small molecule	Investigational	Anti-infective	1. Glutathione *S*-transferase A1 2. Glutathione *S*-transferase P	Virtual screening	Tahir et al. (2019)
Formoterol	DB00983	Small molecule	Approved, investigational	Anti-Asthamatic	1. Beta-2 adrenergic receptor 2. Beta-1 adrenergic receptor 3. Beta-3 adrenergic	Virtual screening	Smith and Smith (2020)

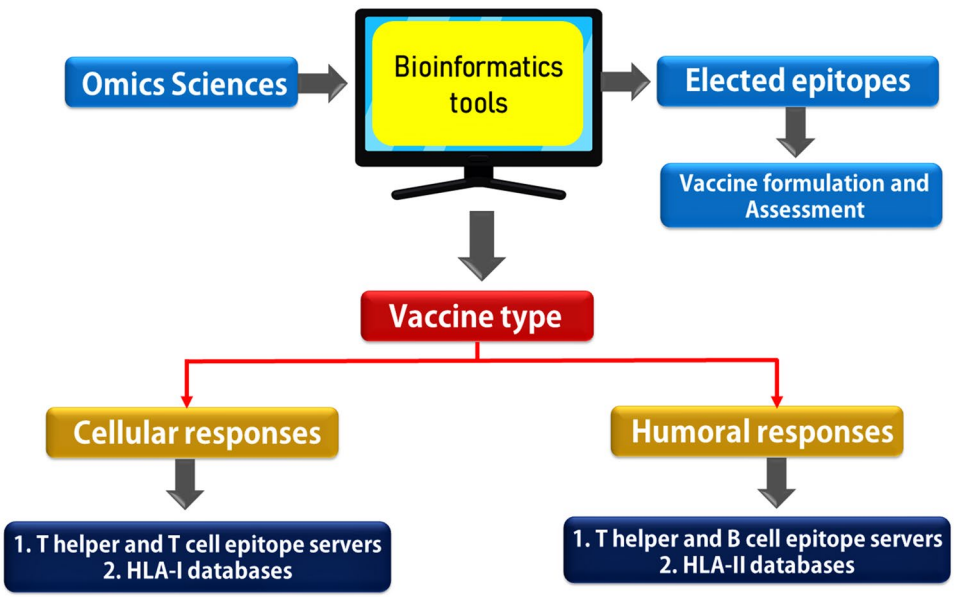

Fig. 4 Schematic representation of in silico vaccine development

In silico designing of ACE2-based peptide inhibitors for COVID-19

It has been reported that the protein fragment spike protein can block the SARS-COV-2 and SARS-COVs entry in human ACE2 expressing cells, respectively. Therefore, it may give the entry inhibition response against COVID-19 infection. It has also been reported in several in vitro and in vivo studies that angiotensin-converting enzyme 2 is the functional receptor of SARS-CoV-2 viral infection. Likewise, it has confirmed that SARS-CoV-2 uses this functional receptor as an entry point in the human host. ACE-2 is the first type of membrane protein expressed in several tissues containing the heart, lungs, intestine, and endothelium cells (Han and Kral 2020). Angiotensin-converting enzyme 2 in epithelial cells can facilitate the viral replication in the lungs and may cause cell damage in infected patients. In identifying receptor-binding domain ACE2, protease remains to engage in alpha-1 helix along with little involvement of alpha-2 helix with beta-3 and beta-4 linkers. The molecular dynamics simulation confirmed that alpha-helix peptides are involved in maintaining the secondary structure and serve highly stable blocking with the SARS-CoV-2. In silico approaches have used to find efficient therapy against covid-19 protease (Basu et al. 2020). Virtual screening of potential compounds across the SARS-CoV-2 spike protein to block the virus from the interaction to the host receptor reveals low molecular weight compounds having high binding affinity. Using classical molecular dynamics approach may also tell that peptide inhibitors isolated from angiotensin-converting enzyme 2 having a highly promising route to block SARS-CoV-2 infection. Therefore, it is suggested that the computational analysis could serve as a potential therapy to identify the antigen and can also form structure-based antibodies designing with high affinity. Even though in silico-based proposed small peptides can also be used as inhale therapeutic to current lung delivery, which may be helpful in combating the SARS-COV-2 infection (Basu et al. 2020).

Complications and clinical outcome

According to current data, several corona-infected patients have a good prognosis while some patients have worse conditions, especially in older candidates having severe diseases (Guo et al. 2020). The patient complications carry multi-organ failure, liver and kidney dysfunction as well as acute lung distress syndrome. Therefore, these adversities were related to wrong clinical conclusions. It is observed in older or neonates the disease was progressing at a very faster rate from the development of the first symptoms. Moreover, the persons above 60-year age having co-existence of other severe conditions and acute respiratory dysfunction syndrome demonstrated a high death exposure. Likewise, the elders and children have more risk in response to immature and poor immune systems (Guo et al. 2020).

Host immune response

The host immune response is essential in controlling and resolving the CoVs-infection; likewise, it can also cause immunopathogenesis via an uncontrolled immune response. The CoVs spike proteins bind with ACE-2 cell receptors in response to invade in the host cell membrane and releases the viral RNA particles (Guo et al. 2020). These RNA particles are recognized via pattern recognition receptors (PPRs). Usually, the foreign DNA or RNA viral particles in endosomes are sensed by TLR3, TLR8, TLR-9, and TLR-7. Likewise, the viral particles in the cytoplasm are detected through retinoic acid 1; Cytosolic receptor melanoma differentiated association gene5 and nucleotidyltransferase cyclic GMP-AMP synthase. These complexes signalling pathways can call up the adaptors containing INF-beta, mitochondrial anti-viral molecules and interferon gene–protein stimulators to activate the downstream cascade response. In these cascades, MYC88 and lead adaptor molecule are involved in the activation of NF-KB and interferon regulatory factor-3. In contrast, the activation of NF-KB and interferon regulatory factor-3 induces the formation of type 1 interferon (alpha/beta) and an array of pro-inflammatory cytokines (Guo et al. 2020). Hence the host–viral interaction can give a vast range of immune responses to distort the invading of viral particles. However, the natural immune response is significant for fighting against pathogens; otherwise, the consequences are immunopathogenesis. In the case of SARS-CoV-2 disease, some plasma cytokines and chemokines were detecting ascended, containing IL2, IP10, IL10, IL7, MIP1A, macrophages, tumour necrosis factor-alpha, and hepatocytes growth factor. An anatomical report of SARS-CoV-2 pneumonia infections expresses that the lower respiratory tract inflammation may cause severe lung injury. It has also been observed that the viral RNA, first of all, invade in lung mucosa and causes the infection to other cells. That infection interferes in the group of immune responses and produces the storm in the human body, which may combine with the severe condition in corona-infected patients (Guo et al. 2020).

Therapy/prevention

Due to a lack of efficient anti-viral drugs against SARS-CoV-2 infection, the current therapy focuses on respiratory and emblematic support. At present no effective anti-viral drugs has been established yet against SARS-CoV-2 infection (Wu et al. 2020). Hence, the repurposed drug use is the only way to fight against these outbreaks. Based on the in vitro identification on cell lines, remdesivir is found to interfere with NSP12 polymerases and has successfully reported as an effective drug against COVID-19 (Ammar et al. 2020). Simultaneously, chloroquine has been declared as an immunomodulator that suppresses the developing TNF-alpha, interleukin-6. This drug involves in triggering the pathogenic replication machinery (Singhal 2020). Therefore, it has been potentially found to fight against SARS-CoV-2 infection. Through in vitro experimentation, the combination of chloroquine and remdesivir drugs has proven to inhibit the SAS-CoV-2 infection accurately (Guo et al. 2020). Moreover, it has also been seen in Korea that viral loads of the SARS-CoV-2 disease reduced significantly after the treatment by a combination of drugs, i.e., lopinavir and ritonavir (Singhal 2020). It is to be noted that until the availability of proper vaccines and medications against COVID-19, our immune system will also require to adapt independently to SARS-CoV-2 infection (Ahmed et al. 2020). Therefore immune boosting will also play a significant role in the prevention of SARS-CoV-2 disease while potentially protecting our body against harmful microbes. Plasma therapy and stem cell therapy are being explored for the treatment against SARS-CoV-2 infection. Several researchers have reported that convalescent plasma treatment could improve the clinical outcomes of the critically infected patients. Plasma therapy has been proved beneficial in several COVID-19 patients in China, though the sample size was small (Tay et al. 2020). Indian Council of Medical Research (ICMR) and Drug Controller General of India (DGCI) have given the nod to Kerala Government in India to conduct clinical trials using plasma therapy. A couple of patients who were in critical condition in the intensive care unit (ICU) were given this treatment in Institute of Liver and Biliary Sciences (ILBS) in New Delhi and patient recovered.

Conclusions

The terrible situation caused by COVID-19 needs immediate remedy. In silico methods can find novel and potential epitopes without taking any risks of cultivating the microbes of interest. This method has advantage in the development of vaccines with faster outcomes and lower costs. To confirm their zoonotic origin, in silico-based sequence analysis reveals that bats are the key reservoir of these viruses. By phylogenetic analysis, researchers found that the human SARS-CoV-2 having more similarity with SARS-like bats Coronaviruses. However, several health researchers are employed to form effective therapeutic plans for fighting against SARS-CoV-2 infection. Nevertheless, no licensed vaccines or drugs are yet available, and the cure is restricted to supportive care with few repurposed drugs. Based on the in vitro identification on cell lines, remdesivir, chloroquine, lopinavir, and oseltamivir were significantly found to inhibit SARS-CoV-2. But to commercialize drugs and vaccines against COVID-19, much more time is required (Ahmed et al. 2020). In this unprecedented situation, various in silico approaches may offer an alternative screening to optimize hits to lead stages. It also provides useful network based pharmacology for finding the repurposed or combination drugs for curing the SARS-CoV-2 infection.

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Compliance with ethical standards

Conflict of interest The authors declared no conflict of interest with respect to the research, authorship, and publication of this article.

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