Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Molecular characterization, pathogen-host interaction pathway and *in silico* approaches for vaccine design against COVID-19

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ABSTRACT

COVID-19 has forsaken the world because of extremely high infection rates and high mortality rates. At present we have neither medicine nor vaccine to prevent this pandemic. Lockdowns, curfews, isolations, quarantines, and social distancing are the only ways to mitigate their infection. This is badly affecting the mental health of people. Hence, there is an urgent need to address this issue. Coronavirus disease 2019 (COVID-19) is caused by a novel *Betacorona virus* named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) which has emerged in the city of Wuhan in China and declared a pandemic by WHO since it affected almost all the countries the world, infected 24,182,030 people and caused 825,798 death as per data are compiled from John Hopkins University (JHU). The genome of SARS-CoV-2 has a single-stranded positive (+) sense RNA of ~30 kb nucleotides. Phylogenetic analysis reveals that SARS-CoV-2 shares the highest nucleotide sequence similarity (~79 %) with SARS-CoV. Envelope and nucleocapsids are two evolutionary conserved regions of SARS-CoV-2 having a sequence identity of about 96 % and 89.6 %, respectively as compared to SARS-CoV. The characterization of SARS-CoV-2 is based on polymerase chain reaction (PCR) and metagenomic next-generation sequencing. Transmission of this virus in the human occurs through the respiratory tract and decreases the respiration efficiency of lungs. Humans are generally susceptible to SARS-CoV-2 with an incubation period of 2–14 days. The virus first infects the lower airway and bind with angiotensin-converting enzyme 2 (ACE2) of alveolar epithelial cells. Due to the unavailability of drugs or vaccines, it is very urgent to design potential vaccines or drugs for COVID-19. Reverse vaccinology and immunoinformatic play an important role in designing potential vaccines against SARS-CoV-2. The suitable vaccine selects for SARS-CoV-2 based on binding energy between the target protein and the designed vaccine. The stability and activity of the designed vaccine can be estimated by using molecular docking and dynamic simulation approaches. This review mainly focused on the brief up to date information about COVID-19, molecular characterization, pathogen-host interaction pathways involved during COVID-19 infection. It also covers potential vaccine design against COVID-19 by using various computational approaches. SARS-CoV-2 enters brain tissue through the different pathway and harm human's brain and causes severe neurological disruption.

1. Introduction

The origin of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 (Singhal, 2020). This virus causes severe pneumonia, a respiratory disease now described as COVID-19 (Coronavirus Disease, 2019) officially declared by the World Health Organization (WHO). International Virus Classification Commission (ICTV) classified novel coronavirus as SARS-CoV-2 (Yang and Wang, 2020). WHO declared COVID-19 as a global pandemic due to uncontrolled transmission and unavailability of the treatment of COVID-19. Coronavirus infected patient shows common symptoms like difficulty in respiration, cough, fever, shortness of breath (CDC, 2020a). The critical condition of this disease is multi-organ damage (lung and kidney) and finally causes the death of COVID-19 suffered person. Generally, lung damage is the main reason for the death of COVID-19 patients (Wu et al., 2020a, b, c, d).

COVID-19 is not the first only disease caused by coronaviruses. In the past two decades, three coronavirus diseases have been reported

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(Mackenzie and Smith, 2020). COVID-19, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) are the three global epidemics caused by a coronavirus (Memish et al., 2020). The outbreak of SARS-CoV disease was reported in 2002–2003 and caused about 8000 infections in humans (World Health Organization (WHO, 2020e). MERS-CoV disease was emerged in 2012 and caused 2106 infection in humans (Memish et al., 2020). Behind the coronaviruses diseases, other viral diseases such as influenza, polio, ebola, AIDS (acquired immunodeficiency syndrome), and hepatitis also affected the human population Worldwide (Mourya et al., 2019). A major outbreak of viral diseases since the early 20th century and their impacts on the human population have been mentioned in Table 1. These viral diseases have caused a large number of infections and death during the period of the 20th and 21 st centuries. COVID-19 is one of the highly transmitted among these diseases. The high transmission rate of COVID-19 might be due to a large incubation period and the structure of spike glycoprotein (Li et al., 2020a, b, c). The novel coronavirus was named as SARS-CoV-2 due to similar characteristics to SARS-CoV. It consists of spike glycoprotein (S), membrane protein (M), an envelope protein (E), nucleocapsid protein (N), and linear single-stranded positive (+) sense RNA of ~30 kb (Fig. 1). The genome study of SARS-CoV-2 shows a close relation with SARS-CoV and MERS-CoV. Phylogenetic analysis revealed that SARS-CoV-2 has emerged from Bat SARS-like CoV because lineage B beta-CoV originated from bat and lineage B beta-CoV share 96 % sequence similarity with SARS-like CoV (Chen et al., 2020a, b). The pathogenic mechanism of SARS-CoV-2 is also very similar to the SARS-CoV as well as MERS-CoV. SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) receptor during entry into the host cell. Same ACE2 receptor expressed during SARS-CoV infection in unciliated bronchial epithelial cells and type II pneumocytes (Qian et al., 2013). MERS-CoV recognizes to dipeptidyl peptidase 4 (DPP4) receptor during infection in human cells (Raj et al., 2013).

Several studies have reported that transmission of SARS-CoV-2 from bat to human via the food chain. Therefore, bats are considered as the primary host of SARS-CoV-2 due to its similarity with bat coronaviruses (Hampton, 2005; Banerjee et al., 2019; Li et al., 2005). Transmission of SARS-CoV-2 human to human mainly occurs through respiratory droplets and close contacts with an infected person. Fig. 2 depicts the mode of transmission of SARS-CoV-2. The mortality rate of MERS-CoV and SARS-CoV is higher than COVID-19 but the transmission rate of COVID-19 is found several times higher compared with SARS-CoV and MERS-CoV (Petrosillo et al., 2020). The higher transmission rate makes it more transmissible and contagious. COVID-19 caused infection in about 241 million people and 8 million deaths as of August 27, 2020, worldwide (Johns Hopkins University (JHU, 2020). United States of America (USA) is the most affected country in the World. The list of most COVID-19 affected countries and current COVID-19 reports in the respected countries have been mentioned in Table 2.

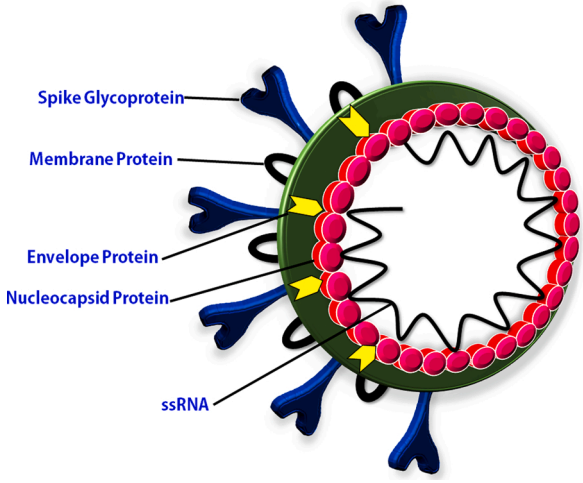

Fig. 1. The structure of COVID-19 which cause SARS-CoV-2.

USA, Brazil, India, Russia, and South Africa are the top COVID-19 affected countries. Across the world, various governing bodies are taking various decisions to stop the spread of the SARS-CoV-2 virus through social distancing and lockdown (Gutiérrez, 2020). The high transmission rates in these countries might be due to late partially or late lockdown and environmental factors such as temperature (Yuki et al., 2020). Early and complete lockdown of the whole country is playing an important role in the reduction of social gatherings and eventually responsible for the low transmission rate in India (Gupta et al., 2020).

There is no specific treatment available for COVID-19. The treatment of COVID-19 symptoms and oxygen supply via mechanical ventilation is the major therapy in the present time (Begley, 2020). Some broad-spectrum antibiotics and plasma therapy are also used for the reduction of viral load but these therapies are unable to eliminate COVID-19 (Mandal, 2020). Hence, a vaccine is a potential option for COVID-19 treatment. The researchers are working to design a potential vaccine for COVID-19. Vaccine development is a very complex process; however, computation biology can design easily potential vaccines (Rahman et al., 2020; Enayatkhani et al., 2020). A designed vaccine based on structural and non-structural viral protein provokes protective immune responses (Dong et al., 2020). Modern bioinformatics

Table 1
Viral pandemic in the 20th and 21st century.

Disease	Year	Infection	Mortality (Estimated death)	Country badly Affected	References
Influenza	1918–19	500 million	2–3 % (50 million)	Killed > half million people in USA	(CDC, 2020b)
Polio	Peak of 1940s & 1950s	42,173	2,720	US, Canada, UK	(Mehndiratta et al., 2014)
Marburg Disease	1967s	24	Up to 88 %	Angola, Congo, Kenya, South Africa, Uganda	(World Health Organization (WHO, 2020d)
Ebola hemorrhagic disease	1970s & 1990s	602	431	Sudan, Yambuku	(Laupland and Valiquette, 2014)
HIV	1980s & 1990s	3,064	1,292	United States	(Healthline, 2020)
Hepatitis	1996	400,000–600,000	300 million	US	(CDC, 2020c)
Lassa fever	1969	300,000–500,000 per year	5000 people	West Africa, Sierra Leone, Guinea	(World Health Organization (WHO, 2020a)
West Nile Fever	2002	4,156	284	Canada, Mexico, Ontario, Quebec	(Chancey et al., 2015)
SARS	2003	8422	11 %	China, Hong Kong, Taiwan	(World Health Organization (WHO, 2020b)
MERS	2012	2500	(35 %) 858	Saudi Arabia	(World Health Organization (WHO, 2020c)
COVID-19	2019	24,182,030	825,798	>210 counties	(Johns Hopkins University (JHU, 2020)

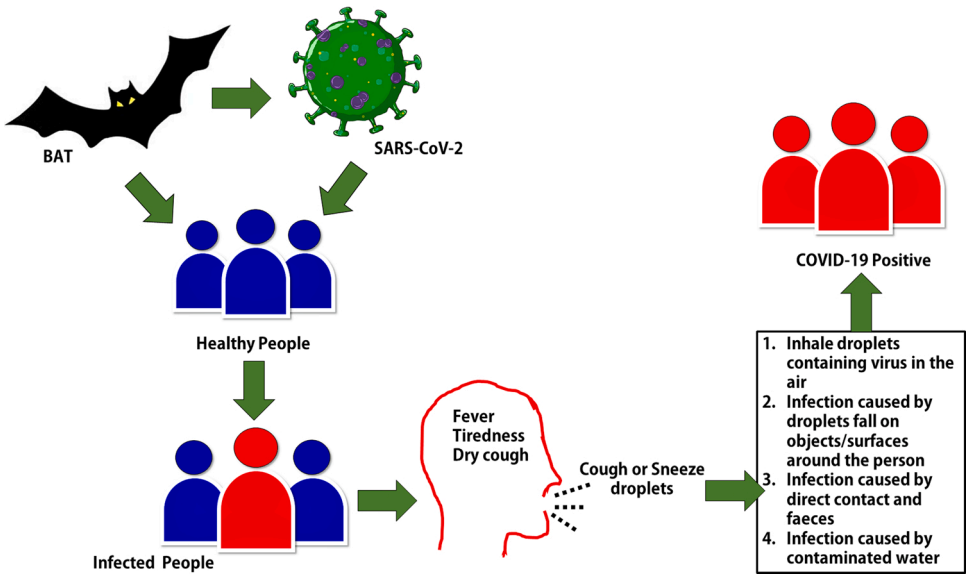

Fig. 2. Transmission and infection of SARS-CoV-2.

Table 2
Mortality and Recovery by COVID-19 in major affected countries till August 27, 2020.

Country	Total confirmed cases	Mortality	Recovery	References
USA	5,822,927	179,735	2,084,465	(Johns Hopkins University (JHU, 2020)
Brazil	3,717,156	117,665	3,082,447	(Johns Hopkins University (JHU, 2020)
India	3,310,234	60,472	2,523,771	(Johns Hopkins University (JHU, 2020)
Russia	968,297	16,638	784,277	(Johns Hopkins University (JHU, 2020)
South Africa	615,701	13,502	525,242	(Johns Hopkins University (JHU, 2020)
Mexico	573,888	62,076	472,197	(Johns Hopkins University (JHU, 2020)
Peru	607,701	28,001	414,577	(Johns Hopkins University (JHU, 2020)
Spain	419,849	28,971	150,376	(Johns Hopkins University (JHU, 2020)
Italy	262,540	35,458	206,329	(Johns Hopkins University (JHU, 2020)
France	291,374	30,549	85,811	(Johns Hopkins University (JHU, 2020)
Germany	239,014	9,290	212,464	(Johns Hopkins University (JHU, 2020)
China	87,363	4,658	80,594	(Johns Hopkins University (JHU, 2020)
Iran	365,606	16,569	261,200	(Johns Hopkins University (JHU, 2020)

approaches for vaccine design are cost-effective, time-saver, and more effective compared to traditional methods (Sieber et al., 2018; Wolf et al., 2010). This review focused on the genomic and molecular characterization of SARS-CoV-2, pathogenic mechanism, and *in-silico* vaccine design. This review also covered up to date information about COVID-19 transmission Worldwide.

2. Molecular characterization

Disease entity of viral infection depends on both molecular and virology techniques including virus isolation and diagnostic test (Ellis and Zambon, 2002). Characterization of SARS-CoV-2 can be accomplished by using molecular approaches. Zhou et al. (2020a, b) reported the characterization and identification of SARS-CoV-2 cause an epidemic of respiratory illness in a human. Zhang et al. (2020) isolated the viral sample from the bronchoalveolar lavage fluid of SARS-CoV-2 infected patients and characterized the viral sample using RT-PCR using degenerate primers and probes designed for detection of SARS-CoV-2. The presence of SARS-CoV-2 in the sample was confirmed by metagenomic sequencing approaches such as high-throughput sequencing (Zhou et al., 2020a, b). The genome size of SARS-CoV-2 was found at about ~30 kb in length (29,891 bp). Comparative genome analysis with other coronaviruses revealed that the virus genome was closely similar to previously characterized coronaviruses. Fig. 3 shows the genome similarity of SARS-CoV-2 with MERS-CoV and SARS-CoV.

Therefore, after the identification of SARS-CoV-2, the phylogenetic relationship among the viruses of the same family was studied using bioinformatics approaches (Ching et al., 2003). The genome size of SARS-CoV-2 was 29,891 nucleotides long which contains 8,903 adenosines, 9,574 uracils, 5,852 guanines, and 5,482 cytosines. The G + C content of SARS-CoV-2 is 32 %–43 %. The genome of SARS-CoV-2 encodes 9860 amino acids. Which are arranged in series of 5′UTR, replicase (orf1a/b), Spike(S), Envelope (E), Membrane (M), Nucleocapsid (N), 3′UTR. The genome of SARS-CoV-2 contains 5′UTR, 3′UTR, and six functional open reading frames (ORFs) such as *ORF1a/b, S, E, M,* and accessory gene including *ORF3b* and *ORF8* (Chan et al., 2020). *ORF1a/b* translates into a polyproteins pp1a and pp1ab. These polyproteins are further processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro) and one or two papain-like protease (PLpro). Papain-like protease cleaved into 16 non-structural proteins which play a role in the replication and transcription of virus infection (Mousavizadeh and Ghasemi, 2020). Serine type protease encoded by nsp5 is the Main protease (Mpro). 3CLpro is dimeric form, and each monomer contains two subunits, the catalytic N-terminal residue, and the C-terminal residue. 3CLpro sequence shares 96 % identity in both SARS-CoV and SARS-CoV-2 (Gil et al., 2020). Various researches it has been reported that the main protease of SARS-CoV-2 plays a significant role in replication, transcription, and translation of viral proteins (Kumar et al., 2020a, b, c). Mpro represents a potential target due to its involvement in essential viral functions (Estrada, 2020). *ORF3b* encoded a completely novel short protein and *ORF8* likely encodes a secreted protein form by alpha-helix followed by beta-sheet contains six strands of the unknown function. *S* gene of SARS-CoV-2 has a sequence identity

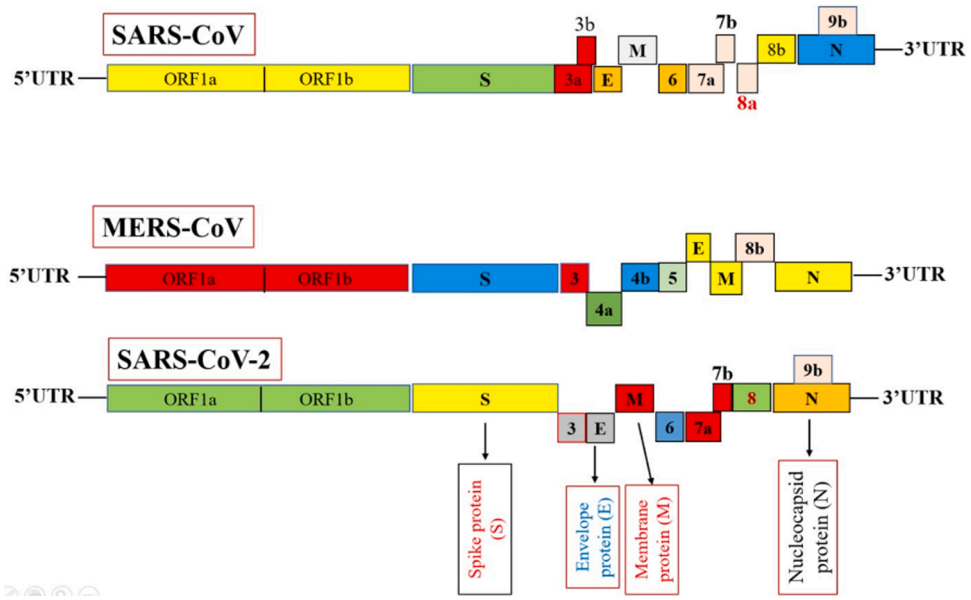

Fig. 3. Genome similarity and dissimilarity among MERS-CoV, SARS-CoV and SARS-CoV-2.

of less than 75 % to bat SARS-like-CoV (SL-CoVZXC21 and SL-CoVZC45) and human SARS-CoV. *S* gene of SARS-CoV-2 encodes spike glycoprotein was longer as compared to SARS-CoV (Zhou et al., 2020a, b; Paraskevis et al., 2020).

From the phylogenetic analysis of coronaviruses, we analyzed that SARS-CoV-2, SARS-CoV, MERS-CoV, HCoV-OC43, and HCoV-HKU1 are beta coronavirus and HCoV-NL63, HCoV- 229E are alpha coronaviruses. Nucleotide sequences of SARS-CoV-2 were retrieved from the National Centre for Biotechnology Information database (NCBI). Multiple sequence alignment of SARS-CoV-2 with reference sequences was done using Clustal W software with the default parameter. Phylogenetic tree analysis of the complete genome using maximum likelihood (ML) method-based Tamura-Nei model was done using MEGA software with 100 bootstrap replicates (Zhou et al., 2020a, b). The obtained phylogenetic tree has been shown in Fig. 4. Multiple sequence alignment is a sequence alignment of more than three biological sequences. It minimizes the number of insertion or deletion (gaps). It is used to reconstruct the phylogenetic tree and show the evolutionary relationship with a common ancestor. Functionally important sites including binding sites, active sites are identified using MSA (Chatzou et al., 2016).

Phylogenetic tree constructed using whole genomes of coronaviruses and it represents the evolutionary relationship among coronaviruses. Several branches show the bootstrap value (100) check the reliability of the tree. Based on a phylogenetic tree, SARS-CoV-2 shares a common ancestor with two other bat SARS-like coronaviruses such as bat-SL-CoVZC45 and bat-SL-CoVZXC21 with 88 % sequence similarity. Because both bat viruses are present in the same cluster which shows monophyletic groups but distantly related from SARS-CoV about 79 % and MERS-CoV about 50 % that shows paraphyletic groups (Zhou et al., 2020a, b).

From previous research, homology modeling shows that SARS-CoV-2 has the same receptor-binding domain as SARS-CoV. Therefore, it confirmed that SARS-CoV-2 uses ACE2 as a receptor, despite the presence of difference in amino acid in the SARS-CoV-2 receptor-binding

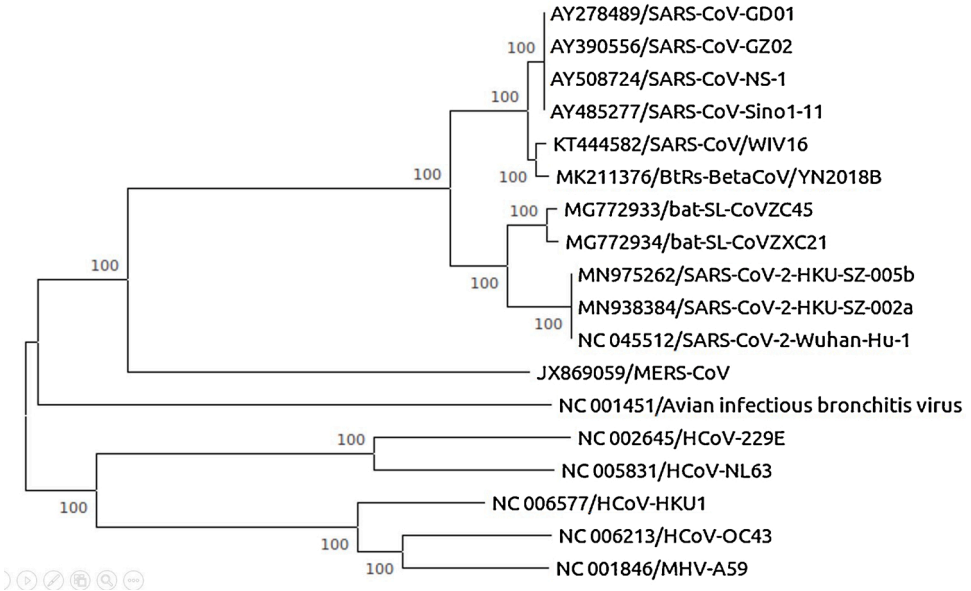

Fig. 4. Phylogenetic tree of coronaviruses using MEGA software.

domain (Walls et al., 2020). Based on virus genome sequencing and phylogenetic analysis, the bat is considered as the primary source and origin of SARS-CoV-2 (Zhou et al., 2020a, b).

3. Host-pathogen interaction

The SARS-CoV-2 is first reported from the wild animal market of Wuhan city. The bat is considered as the primary host of SARS-CoV-2 due to close genome similarity with bat SARS-CoV-2 (Huang et al., 2020). The previous study (Cyranoski, 2020) suggested that pangolins are the intermediates host of SARS-CoV-2. Isolated virus from pangolins showed 99 % genome similarity with the human SARS-CoV-2. The COVID-19 transmission in animal to human was due to the consumption of COVID-19 infected animals as food. After entering into the human host, SARS-CoV-2 is transmitted rapidly in the human population. The most probability of transmission of SARS-CoV-2 from human to human is via respiratory droplets and close contacts with respiratory symptoms (Chan et al., 2020). As of August 27, 2020, a total of 24,182,030 confirmed cases were reported worldwide with total death of 825,798 (Johns Hopkins University (JHU, 2020). The high transmission rate of SARS-CoV-2 might be due to the spreading of the virus via asymptomatic-infected person and some modifications in the spike proteins (S) (Rothe et al., 2020). The Spike protein (S) plays an important role in virus attachment, fusion, and entry. The spike glycoproteins (S) are also considered as potential target sites for antiviral drugs and vaccines. Receptor binding domain (RBD) presents in the spike protein of SARS-CoV-2 and is strongly bound to the human ACE-2 (Tai et al., 2020). Hence, SARS-CoV-2 used angiotensin-converting enzymes 2 (ACE2) for entry purposes into the host cell. ACE2 express on the cell surface of a wide range of animals including human. ACE2 could help in the interspecies and human to human transmission of COVID-19 (Hoffmann et al., 2020).

The recent study defined the more accurate COVID-19 transmission situation and outbreak in the future. Researchers use a mathematical model to define reproduction number (R_0) which is related to the spreading of COVID-19 from one infected person. If R_0 is below 1, it indicates that disease can spread in half of the persons through COVID-19 infected person and disease is considered as in controlled situation. If the value of the R_0 is more than 1, it indicates that the disease is very contagious and considered under an uncontrolled situation (Thompson, 2020). Liu et al. (2020) reported 3.28 average R_0 of COVID-19 in China from the period between January 1, 2020, to February 7, 2020. This indicates COVID-19 is an uncontrolled and highly infectious disease. SARS-CoV-2 has a high R_0 comparison with SARS-CoV ($R_0 = 1.4$) and MERS-CoV ($R_0 = 2.5$), indicates that SAR-CoV-2 is more spreadable than SARS-CoV and MERS-CoV and may cause a global pandemic (Li et al., 2020a, b, c; Wu et al., 2020a, b, c, d). The majority of COVID-19 patients suffered only lung infection because it is only associated with respiratory disease. The asymptotic incubation period of COVID-19 varies from 2-14 days (Wu et al., 2020a, b, c, d; Chen et al., 2020a, b).

3.1. SARS-CoV-2 entry and intracellular replication

The entry of SARS-CoV-2 into the human host cells through upper body opening like mouth and nasal opening. SARS-CoV-2 recognizes to host cell receptors such as ACE2 present on the outer membrane of the host cell (Zhou et al., 2020a, b; Jia et al., 2005; Wan et al., 2020). Current studies by Lan et al. (2020) reported that the receptor-binding domain (RBD) in the SARS-CoV-2 spike protein strongly binds to ACE2 with higher affinity. The summarized mechanism of viral-host interaction has been shown in Fig. 5. The figure shows the viral host interaction and multiplication of viruses within the host cell. This figure shows the entry and replication of the viral genome of SRAS-CoV-2 virus and synthesis of the SARS-CoV-2 virus in the endoplasmic reticulum by using viral component and finally release of viral particle (complete viruses) via exocytosis.

Receptor binding domain (RBD) on the surface of SARS-CoV-2 binds to ACE2 on the surface of the host cell receptor (Tortorici and Veesler, 2019). The direct membrane fusion between virus and plasma membrane also reported the second entry mechanism of entry of SARS-CoV into the host cell (Simmons et al., 2004). Belouzard et al. (2009) reported the proteolytic cleavage of ACE2 protein during nitration of viral spike protein and host receptor (ACE2). After entry of the viral RNA genome into the host cell cytoplasm, it starts to synthesize some important viral proteins such as pp1a and pp1ab. The positive-sense viral RNA also enter start to replicate and form multiple viral genomes

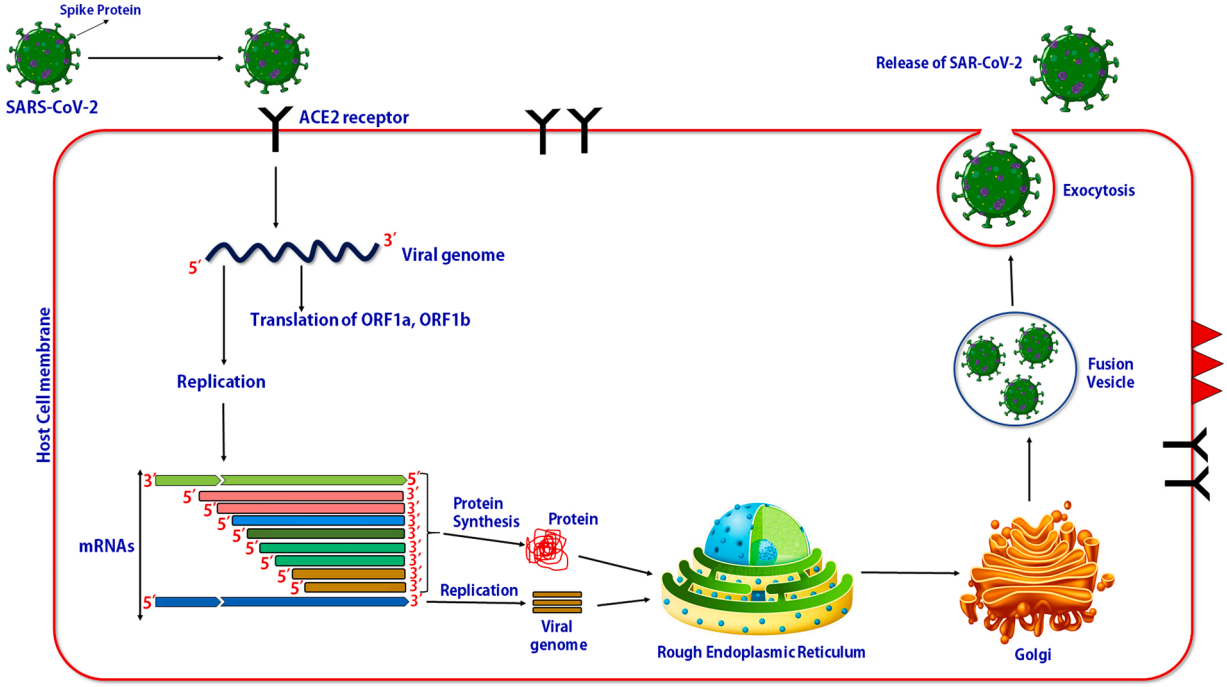

Fig. 5. Viral host interaction and multiplication of viruses within host cell.

(Xia et al., 2020; Yu et al., 2020; de Wilde et al., 2018; Perlman and Netland, 2009). Translated viral protein enters into the rough endoplasmic reticulum and Golgi complex for post-translational modification. The newly synthesized viral RNA and protein form complete viral particles assembled into fusion vesicles. These vesicles fused with the plasma membrane and virus particles come out from the host cell and target to next healthy (de Wit et al., 2016).

3.2. Antigen presentation during coronavirus infection

When a virus enters the host cell, its antigen is presented on the antigen-presenting cells (APCs). The antigen presentation of the viral antigen plays an important role in ant-viral immunity. HLA (human leukocyte antigen) and MHC (major histocompatibility complex) are the major antigen-presenting cells for SARS-CoV-2 antigen. The viral antigen is presented by HLA and MHC and is recognized by CTLs (cytotoxic T lymphocytes). Understanding the mechanism of the antigen presentation might be helpful in drug development and vaccine design. The similar receptor expression and antigen presentation also occur in the SARS-CoV (Liu et al., 2010). The gene polymorphism of mannose-binding lectin also correlated with the SARS-CoV-2 infection (Tu et al., 2015). These studies will be provided with important clues for understanding the pathogenic mechanism and treatment for COVID-19.

3.3. Anti-viral immunity and cytokine storm

Viral antigen stimulates viral-specific B and T cells. Two viral-specific antibodies IgM and IgG produced in COVID-19 infection after 1st week of infection. However, IgM antibodies disappeared after 12 weeks of viral infection but IgG remained for a long time, this indicates that IgG is the main antibodies for viral infection (Li et al., 2003). IgG antibody is specific for S and N antigen of SARS-CoV-2 (de Wit et al., 2020). The latest report shows that the portion of CD4+ and CD8+ significantly decreases in the peripheral blood in SARS-CoV-2 patient, whereas its status is excessive activation, as evidence by the high number of HLA-DR (CD3.47) and CD38 (CD8 39.4 %) in double-positive fraction (Xu et al., 2020). CD4+ and CD8+ cells can persist up to four years after SARS-CoV infection and can perform T cell proliferation and IFN-Ɣ production (Fan et al., 2009). The CD8+ cell performs the same mechanisms in the MERS-CoV-2 (Liu et al., 2017, 2006).

The ARDS (acute respiratory distress syndrome) is the main death cause of COVID-19 infection. It is the common immunopathological events in the MERS-CoV, SARS-CoV, and SARS-CoV-2 (Xu et al., 2020). The mechanism of the ARSD is based on cytokine storm in which release of the uncontrolled amount of pro-inflammatory cytokines such as IFN-α, IFN-Ɣ, IL-6, etc (Cameron et al., 2008; Channappanavar and Perlman, 2017). Uncontrolled cytokine is responsible for the violent immune attack and causes damage to multiple organs. The SARS-CoV-2 patient died due to damage to the lungs and in some cases kidney and liver damage (Xu et al., 2020).

4. Treatment of COVID-19

There is no specific anti-viral treatment for COVID-19 and no vaccine available. Currently, the treatment of symptomatic and mechanical ventilation (for oxygen supply) is the major treatment option for patients suffering from COVID-19 infection (Mahmud et al., 2020). Nowadays, some broad-spectrum antibiotics such as favilavir and remdesivir also are used to reduce the viral load. Behind this, few other drugs such as lopinavir, ritonavir, and chloroquine are also considered as an option for COVID-19 treatment. Remdesivir (GS5734) is an RNA polymerase inhibitor and has *in vitro* activity against RNA viruses, including Ebola and MERS-CoV infection. This drug is also considered an option against COVID-19 infection (de Wit et al., 2020). Plasma therapy is based on recovered COVID-19 patients and has promising applications in COVID-19 treatment. Vaccination is the basic and effective treatment of this global pandemic but vaccine formation is under development and needs furthermore investigation (Kumar et al., 2020a, b, c). Food and Drug Administration (FDA) approved the clinical study of COVID-19 infected patients to test the safety and efficacy of umbilical cord-derived mesenchymal stem cells to stop the lung inflammation (EPR, 2020). MSCs therapy prevents the extra production of the immune system. Through intravenous infusion, after entering the human body in the lung MSCs accumulated, which protects the pulmonary microenvironment, improve alveolar epithelial cells, inhibit pulmonary fibrosis and protects lung function (Leng et al., 2020). current options of COVID-19 treatment are summarized as:

4.1. Anti-viral drug

There are no effective drugs available for the complete treatment of COVID-19. However, some broad-spectrum antivirals are used for COVID-19 symptoms as well as reducing viral load. The drugs which have an effective role against SARS-CoV, MERS-CoV, Ebola, HIV, and malaria parasites are also used against COVID-19 (Wang et al., 2020). Remdesivir and protease inhibitors nucleotide analogue is used as a treatment for SARS-CoV-2 (Agostini et al., 2018). A combination of Remdesivir with chloroquine or interferon beta is highly effective for the prevention of SARS-CoV-2 infection (Wang et al., 2020). This combination has not caused any side effects during treatment (Wang et al., 2020; Sheahan et al., 2020; Holshue et al., 2020). Hydroxychloroquine is the analogue of chloroquine and having some additional safety aspect comparison to chloroquine. Hydroxychloroquine is widely used for the treatment of COVID-19 (Singh et al., 2020). The government of India exports hydroxychloroquine medicine to some COVID-19 affected countries like the United State of America (USA) and Afghanistan (The Economic times, 2020). Nowadays, Favilavir and Remdesivir are the most effective antibiotic comparisons to other anti-viral drugs and are considered as an option for COVID-19 treatment.

4.2. Plasma therapy and monoclonal antibodies

Plasma therapy is the type of passive therapy in which immunity forms against COVID-19 recovered patients directly or indirectly used for the treatment of a patient suffering from COVID-19 infection (Zhao and He, 2020). When the SARS-CoV-2 pathogen enters into the body of a person, the immune system of that person is recognized as foreign and form immunity against COVID-19. The antibodies (IgM and IgG) formation starts during the second week of infection and the patient shows recovery after the second week of COVID-19. The COVID-19 specific antibodies and other immune components such as memory cells remain in the plasma of the recovered patients. The plasma collects from the recovered per and for COVID-19 after several purification stages (Buonaguro et al., 2020). Plasma therapy has been proved beneficial in several critically SARS-CoV-2 infected patients in China and India.

Anti-SARS-CoV-2 therapy includes monoclonal antibodies block viral RNA, the viral protein which involves the replication and translation, and prevents COVID-19 infection (Zumla et al., 2016). S protein contains two subunits S1 and S2. S1 is the amino N-terminal receptor-binding subunit and S2 is the carboxy C-terminal membrane fusion subunit (Gui et al., 2017). The location of the protease cleavage site is S1/S2 junction which required activation of membrane fusion and virus entry (Testa et al., 2020). Targeting the S1 protein by the generation of neutralizing monoclonal antibodies and S2 targeted the fusion inhibitors may be essential therapeutics to kill the coronaviruses (Zumla et al., 2016). In Italy, great investigation on tocilizumab for the treatment of COVID-19. It is generally used in the treatment of rheumatoid arthritis and considered a promising role in COVID-19 treatment. This investigation is performing by the Istituto Nazionale Tumori, Fondazione Pascale di Napoli of Italy.

4.3. Stem cell therapy

In COVID-19 patients, cytokine storm is the production of a large number of cytokines and immune cells. Mesenchymal stem cell therapy stops the production of the storm release of cytokines by the immune system and enhances the endogenous reparative function of the stem cells. (MSCs) treatment for COVID-19 patients has been started recently in several countries such as China, the USA, Iran, and Jordon. In a previous study, mesenchymal stem cell therapy has been widely used in type 2 diabetes, autoimmune disease, spinal cord injury, graft-versus-host disease (GVHD), and several other diseases. MSCs are multipotent cells present in the different locations of the body such as bone marrow, placenta, and umbilical cord. MSCs have powerful immunomodulatory and regenerative properties (Golchin et al., 2020). After MSCs therapy, the number of peripheral lymphocytes was increased, the C-reactive protein decreased, and cytokine-secreting immune cells activated such as CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3 + NK cells disappeared on day 3−6. also, a group of CD14+CD11c + CD11bmid regulatory DC cell population dramatically increased. The level of TNF-α was significantly decreased at the same time while increased the level of IL-10 in the MSCs treatment group compared with conventional therapy. Also, the gene expression profile showed that MSCs were ACE2- and TMPRSS2- which showed that MSCs are free from COVID-19 infection. Thus, the intravenous transplantation of MSCs was safe and effective for the treatment of COVID-19 infected patients, especially for the patients in critically severe conditions. MSCs stop the viral infection due to cytokine's improved qualities (Leng et al., 2020).

4.4. Vaccine for COVID-19

SARS-CoV-2 which emerged in Wuhan city in December 2019 to date has been transmitted all over the World. The transmission of COVID-19 is uncontrolled due to the absence of effective and complete treatment. Currently, antiviral drugs and other therapies are unable to cure this global pandemic (Chakraborty et al., 2020). Hence, there is an urgent public need to develop a suitable vaccine. The vaccine development of COVID-19 started after the sequencing of SARS-CoV-2 and was published in January 2020. Nowadays, various pharmaceutics and drug companies working with collaboration with the research institute to develop an effective vaccine for COVID-19. It is a time-dependent process and needs to pass several clinical trials (Scavone et al., 2020). The example of some COVID-19 vaccines has been given in Table 3. These vaccine candidates are underdeveloped in several phases.

Moderna therapeutics developed a vaccine and started clinical trials of mRNA-based vaccine (mRNA-1273) just after 2 months of sequence identification (Moderna, 2020). Thanh et al. (2020) described the platforms for vaccine development based on mRNA that provides the flexibility for antigen manipulation and rapid development process. Recombinant protein-based vaccine development may be advantageous owing to typical large-scale production capabilities. The use of an adjuvant can be important in this global pandemic situation. Adjuvants are small molecules that facilitate the immune reaction. Thereby reducing the amount of antigen protein required per dose. This method is more appropriate for COVID-19 vaccine development (Thanh et al., 2020).

These above-mentioned vaccine candidates are under several phases of clinical trials. Their vaccines may be taking more time (several months or years) until complete development. Hence, it is an urgent

Table 3
Potential vaccine for COVID-19 in clinical trials.

Vaccine name	Platform	Type of vaccine	Company name	Clinical phase	References
ChAdOx1 nCoV-19	Non-replicating viral vector	ChAdOx1	University of Oxford/AstraZeneca	Phase-III (24ISRCTN8995144)	(World Health Organization (WHO, 2020f)
mRNA-1273	RNA	Lipid nanoparticle dispersion encapsulated mRNA	Moderna therapeutics	Phase-III (NCT04470427)	(World Health Organization (WHO, 2020f)
Sinovac	Inactivated viral vaccine	Inactivated viral vaccine	Sinovac	(NCT04456595)	(World Health Organization (WHO, 2020f)
Beijing Institute of Biological Products/ Sinopharm	Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	(ChiCTR2000034780)	(World Health Organization (WHO, 2020f)
Wuhan Institute of Biological Products/ Sinopharm	Inactivated viral vaccine	Inactivated vaccine	Wuhan Institute of Biological Products/Sinopharm	(ChiCTR2000034780)	(World Health Organization (WHO, 2020f)
BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	(NCT04368728)	(World Health Organization (WHO, 2020f)
Ad5-nCoV	Non-replicating viral vector	Adenovirus type 5 vector	CanSino biologics	Phase-II (ChiCTR000031781)	(World Health Organization (WHO, 2020f)
RBD-Dimer	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui ZhifeiLongcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	(NCT04466085)	(World Health Organization (WHO, 2020f)
INO-4800	DNA	DNA plasmid encoding S protein delivered by electroporation	Inovio Pharmaceuticals, CEPI	Phase-I (NCT04336410)	(National Institutes of Health (NIH, 2020)
LV-SMENP-DC	Antigen-specific CTLs	Dendritic cells modified with a lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	Shenzhen Geno-Immune Medical Institute	Phase-I Phase-II (NCT04276896)	(National Institutes of Health (NIH, 2020)
Covid-19/aAPC	Pathogen-specific aAPC	aAPCs modified with a lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Shenzhen Geno-Immune Medical Institute	Phase-I (NCT04299724)	(National Institutes of Health (NIH, 2020)

need to develop a potential vaccine against COVID-19 as soon as possible. In this pandemic situation, modern computation approaches may be more effective and less time-consuming compare to traditional approaches.

5. *In silico* approaches for vaccine design

The traditional vaccine takes months or years of trials and also very expensive. Therefore, vaccine design using bioinformatics resources is more advantageous due to cost-effective and time saver. Biological information is well organized present in genetics, biotechnology, and molecular biology and bioinformatics resources stored the biological data and information (Orozco et al., 2013). Bioinformatics approaches including structural analysis, MD simulations, and molecular docking are also used for vaccine design. The overview of vaccine design using bioinformatics approaches are shown in Fig. 6.

In the current situation, vaccine development is an urgent need of the World. The drawback of traditional vaccine development techniques will be overcome by using computational approaches. Immunoinformatic approaches are more useful such as reverse vaccinology, epitope prediction, and structural vaccinology including rational approaches that are required for potential vaccine candidates. Protein scaffolding and epitope prediction play an essential role in vaccine design. Bioinformatics tools are also used for potential vaccine design against new emerging diseases. The vaccine can be designed against COVID-19 based on SARS-CoV, which has a high genetic similarity with the SARS-CoV-2 (Ahmed et al., 2020). Several bioinformatics approaches can be used to design a potential vaccine against COVID-19.

5.1. Reverse vaccinology

Reverse vaccinology (RV) technology is useful for epitope mapping and monovalent peptide vaccine prediction. In reverse vaccinology, a novel antigen of the virus is detected through entered proteome of SARS-CoV-2 using bioinformatics tools. Vaxign reverse vaccinology tool is used for developing a suitable vaccine to fight against SARS-CoV-2 (Sarkar et al., 2020).

5.1.1. Vaccine adjuvants

Peptide-based vaccine adjuvants can be identified by using VaxinPAD. It is used to predict Antigen-presenting cell (APC), epitope, or immuno-modulatory peptides. It made up of aluminum to enhance the host immune response and play a major role in vaccine development (Tom et al., 2019). Adjuvants can be designed by a different component such as TLR4 agonists, T-helper agonists, and flagellin. Toll-like receptors (TLRs) can be used as adjuvant it enhances immune response (Mbow et al., 2010; Kanzler et al., 2007). TLR3 and TLR4 play an important role in pathogen recognition and enhances the innate immune system. Agonists of Toll-like receptors 3 and 4 (TLR3 and TLR4) are potential adjuvant for different vaccines. The mechanism of the adjuvant action of TLR3 and TLR4 agonists is largely associated with their ability to activate APCs

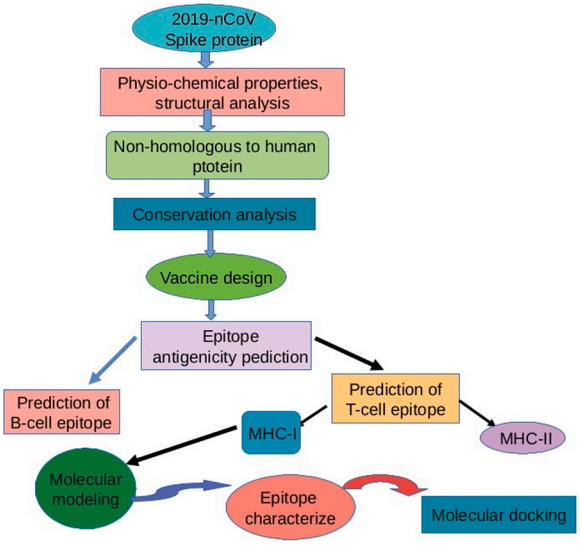

Fig. 6. Application of computational biology in COVID-19 vaccine development.

5.2. Epitope prediction tools

An epitope is part of the antigen to which antibody binds and is recognized by the host immune system. Immunoinformatic tools are used to predict B-cell epitopes, T-cell epitopes, MHC binders, and vaccine adjuvant. Immune epitope database (IEDB) is a repository database that contains available antigenic regions or experimentally validated epitopes that tend to regulate the immune system. IEDB is used for the prediction of B-cell and T-cell epitope (Beaver et al., 2007). Epitope prediction tools design potential vaccines as the epitope stimulate immune cells by both B-cell and T-cell (Kreiter et al., 2015). Several bioinformatics approaches such as support vector machine, neural network, hidden Markov models, and QSAR (quantitative structure-activity relationship analysis) approaches are used to analyze the peptide interactions.

5.2.1. B-cell epitopes

The amino acid sequences of B-cell epitopes analyze using the BepiPred server. It is based on both the hidden Markov model and the amino acid propensity scales method. Kumar (2020) performed vaccine design and the author reported that B-cell epitope VLLPLVSSQCVNLTTRTQLPPAYTN has high antigenicity property. This antigenic epitope considers as suitable for vaccine candidates and developed vaccines could be helpful in viral control.

5.2.2. T-cell epitopes

Immunoinformatic tools such as CTLPred predicted Cytotoxic T lymphocytes (CTL) are useful tools. It is evaluated by an artificial neural network and support vector machine. The major histocompatibility complex plays an important role in the human immune response. It expresses on the cell surface and binds to antigenic peptides. ProPred 1 and ProPred tools are used in the identification of MHC-I and MHC-II binders, respectively (Patronov and Doytchinov, 2013).

5.2.3. Multi-epitope prediction

A multi-epitope-based peptide vaccine can be designed against SARS-CoV-2 using immunoinformatic approaches.

AAY linker is used to link the CTL epitope, GPGPG linker used for HTL epitope, and B KK linker used for the B-cell epitope. EAAAK linker is used to increase the vaccine immunogenicity by adjoining the β-defensin (45 mer) amino acid sequence and pan-HLA DR binding epitopes (13aa) to the N-terminal of the vaccine. The β-defensin adjuvant boosts innate immunity cells and recruits naive T cells with the help of chemokine receptor-6 (CCR-6). Different linkers (AYY, KK, and GPGPG) play potential roles in producing flexibility, protein folding, and separation of functional domains, and therefore, make a more stable protein structure (Dong et al., 2020; Kumar et al., 2020a).

5.3. Allergenicity and antigenicity prediction

The allergenicity of selected protein can be predicted using AllerTOP (https://www.ddg-pharmfac.net/AllerTOP/) and AllergenFP (http://ddg-pharmfac.net/AllergenFP/) are two online tools. AllerTOP prediction tool gives more appropriate results because it has better accuracy (88.7 %) compared to AllergenFP (87.9 %). Antigenicity of designed

protein can be predicted using VaxiJen server. ToxinPredserver tools are based on SVM and this tool applies to the prediction of toxicity of designed proteins. After antigenicity, toxicity and allergenicity tests the protein found as antigenic, non-allergenic, and non-toxic. This protein considers as the best potential for vaccine design (Dimitrov et al., 2013).

5.4. Physicochemical parameters analysis

The physicochemical parameters are molecular weight, isoelectric point (pI), extinct coefficient, aliphatic index, grand average of hydropathicity, stability, and instability index of designed vaccine evaluated by ProtParam online server (Gasteiger et al., 2005).

5.5. Molecular docking

Molecular docking approaches performed the study of molecular interaction for vaccine development (Kumar et al., 2020a, b, c). Molecular docking assays have been widely applied to study and understand the mechanistic interaction of drugs with target protein receptor (Kumar et al., 2020a, b, c). Molecular docking was performed using Autodock Vina and molecular interaction analysis was done using the Autodock tool. Autodock is an automated docking tool it is used to predict how small molecules such as drugs bind to the 3D structure of the receptor. Molecular docking analyses were executed using the Hex 8.0 module. Hex server is a protein docking server based on a fast Fourier transform. Molecular docking used for prediction of binding affinity of chimeric peptide vaccine with immune receptor including TLR3 and TLR4 (Rahman et al., 2020; Saha and Prasad, 2020). Discovery studio visualizer software is used for the determination of the best result of molecular docking (Ullah et al., 2020).

5.6. Molecular dynamics simulation

Molecular dynamics simulation approaches help in analyzing the stable binding of drugs with the target protein. It evaluates the stability of the receptor-ligand complex. Molecular dynamics simulation studies were performed for a long time and analyzed root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and radius of gyration (RG) plots (Kumar et al., 2020a, b, c). With the help of RMSD, RMSF, RG, and other parameters help in analyzing the atomic fluctuations of the interaction complex system (Kumar et al., 2020a, b, c). RMSD plot was determined to analyze each residue dynamics of the target receptor. (RMSF) was obtained for amino acid side chains to analyze the fluctuations of amino acid in the docked complex (Ojha et al., 2020). Molecular dynamics simulation performed by GROMACS 2018 package and iMODS server. GROMACS is one of the fastest molecular dynamics packages for simulation of lipids, proteins, and nucleic acids. iMODS is an online server, it predicts the deformability, B-factor (mobility profiles) and eigenvalues, variance and co-variance and elastic network of protein. The lower eigenvalue shows the deformability of the complex. This server uses for the analysis of protein flexibility (Kovacs et al., 2004).

5.7. Codon optimization and other available tools

The codon optimization method is used for the enhancement of the expression of vaccine protein. Codon Optimization Online (COOL) tool to synthesize genes. A COOL tool is used for the optimization of various parameters (codon optimization parameters) such as codon adaptation, codon pairing, and codon usage (Chin et al., 2014). Codon adaptation is important to step *in silico* cloning, which predicts the best codon for a specific amino acid. Java Codon Adaptation Tool uses for codon adaption and plays an important role in the prediction of protein sequence for potential vaccine design (Grote et al., 2005).

6. Role of COVID-19 on brain tissue

COVID-19 influences the lungs as well as focus on the sensory system. SARS-CoV-2 may arrive at the brain tissue through a neural route from lung chemoreceptors, seriously influencing the cardiorespiratory center (Li et al., 2020a, b, c). SARS-CoV-2 additionally influence the olfactory nerve terminal in the nasal hole. Furthermore, SARS-CoV-2 may come to the cerebral vasculature through the overall flow, breaking the blood-brain barrier and attacking and harming the cerebrum parenchyma. SARS-CoV-2 may bind to its receptor Angiotensin-Converting Enzyme 2 (ACE2) communicated in endothelial cells of cerebral vessels, and inside the brain parenchyma in the two neurons and microglia. Since the blood-brain barrier is disturbed in hypertension and hypertension is continuous comorbidity for COVID-19, these patients may have a higher danger of cerebral complexities. The SARS-CoV-2 infects brain tissue and causes a serious neurological interruption. The main organs and routes of SARS-CoV-2 neuroinvasion are shown in Fig. 7.

As indicated by ongoing investigations, the coronavirus displays neurotropic qualities and instigates neurological diseases. It likewise announced that the SARS-CoVs-2 infection could found in the human cerebrum. The coronavirus disease modifies the CNS and can lead the host immune response to triggers into a steady issue prompting neurological signs. The infected patients assessed right on time for neurological manifestations with migraines, thinking brokenness, paraesthesia, and other pathologic side effects (Wu et al., 2020a, b, c, d). Because of the pandemic, the antagonistic psychosomatic result is expected to increment among people. The virus can also enter the cerebrum through contaminating endothelial cells lining brain vasculature; an electron-microscopic analysis of the frontal lobe distinguished SARS-COV-2 viral particles in the endothelium with some indications for virus transit to the neuropil. The SARS-COv-2 can enter the CNS utilizing the perivascular spaces of the lymphatic system. Moreover, viruses can attack the brain through different nerves, such as the trigeminal nerve, which ventures nociceptive terminals to nasal cavities. Similarly, tactile filaments of the vagus nerve, that innervate the respiratory tract, can introduce another attack route. Additional proof of the SARS-CoV-2 neuro-infection, oedema, and neuronal degeneration were accounted for in posthumous mind tests, while for a situation of encephalitis genome sequencing affirmed viral nearness in the cerebrospinal fluid (Li et al., 2020a, b, c). Researchers have discovered that organoids (little tissue culture produced using human cells that stimulate entire organs) known as "mini-brains" can be infected by the SARS-CoV-2 that causes COVID-19 (IndiaTV, 2020). Structure and function of spike protein are highly important for cell infection and entering the brain cells

7. Conclusion

COVID-19 has brought the entire planet to its knee challenged the entire mankind in various aspects which include health system, economy, research, and development, etc. SARS-CoV-2 emerged in the wild animal market of Wuhan city, China, and currently transmitted all over the World. WHO declared COVID-19 as a global emergency based on its infectious properties. Human to human transmission of COVID-19 occurs through respiratory droplets and human close contact. The transmission rate of COVID-19 is much higher compared to other diseases such as SARS-CoV and MERS-CoV caused by coronaviruses. WHO and other health organizations suggested the lockdowns, curfews, isolations, quarantines, and social distancing as the ways to mitigate transmission of infection. Based on the genomic study, the SARS-CoV-2 is very similar to SARS-CoV and MERS-CoV viruses. Phylogenetic analysis reveals that SARS-CoV-2 shares the highest nucleotide sequence similarity (79 %) with SARS-CoV. The characterization of the SARS-CoV-2 is based on the PCR and metagenomic next-generation sequencing. The pathogenic mechanism of SARS-CoV-2 is very similar to the SARS-CoV virus. SARS-CoV-2 first infects the lower airway and uses the ACE-2 receptor the

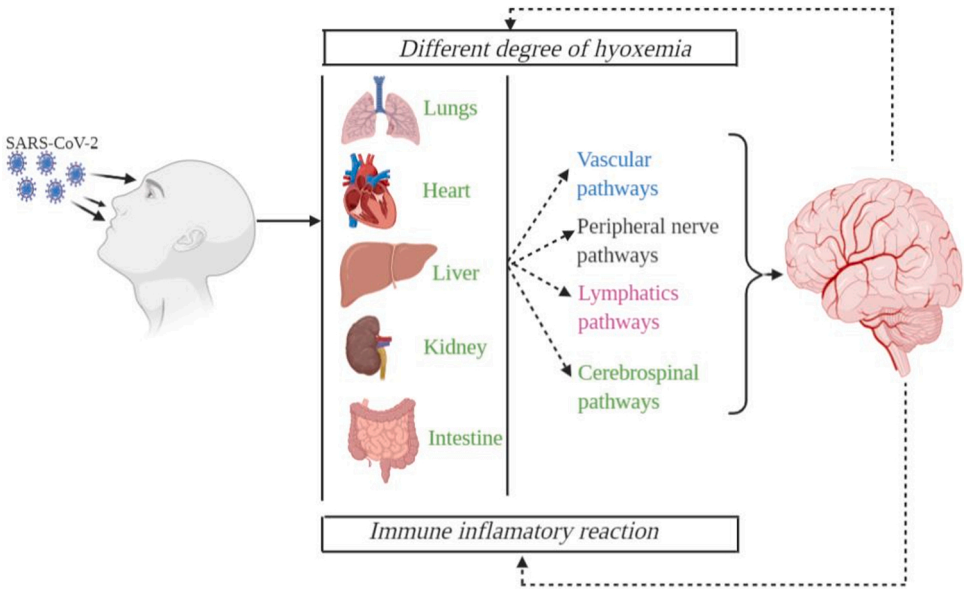

Fig. 7. Main organs and routes of SARS-CoV-2 neuroinvasion. The SARS-CoV-2 enters into body and binds with ACE-2 receptors presents in the cells of major vital organs such as heart, lungs, kidney, liver. SARS-CoV-2. SARS-CoV-2 activate intrinsic immune response, ARDS as well as damage of peripheral tissue. SARS-CoV-2 invasion in the brain through cerebrospinal fluid pathways, lymphatics pathways, peripheral nerve as well as vascular pathways.

same as SARS-CoV. Due to the unavailability of any drug or vaccine, it is needful to design potential vaccines or drugs for COVID-19. Computational methods for design the COVID-19 vaccine are more appropriate compared to traditional methods due to cost-effective, time saver, and more specificity. Immunoinformatics, reverse vaccinology, and molecular docking is major approaches for vaccine development. This review concluded brief information about COVID-19, transmission, genomic and molecular characterization, the pathogenic mechanism of COVID-19, and current treatment option. It also covers potential vaccine design against COVID-19 by using bioinformatics approaches. Infected patients with SARA-CoV-2 should be evaluated early for neurological symptoms, including headache, consciousness disorder, paraesthesia, and other pathological signs

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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