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SARS-CoV-2 spike protein and RNA dependent RNA polymerase as targets for drug and vaccine development: A review

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ABSTRACT

The present pandemic has posed a crisis to the economy of the world and the health sector. Therefore, the race to expand research to understand some good molecular targets for vaccine and therapeutic development for SARS-CoV-2 is inevitable. The newly discovered coronavirus 2019 (COVID-19) is a positive sense, single-stranded RNA, and enveloped virus, assigned to the beta CoV genus. The virus (SARS-CoV-2) is more infectious than the previously detected coronaviruses (MERS and SARS). Findings from many studies have revealed that S protein and RdRp are good targets for drug repositioning, novel therapeutic development (antibodies and small molecule drugs), and vaccine discovery. Therapeutics such as chloroquine, convalescent plasma, monoclonal antibodies, spike binding peptides, and small molecules could alter the ability of S protein to bind to the ACE-2 receptor, and drugs such as remdesivir (targeting SARS-CoV-2 RdRp), favipir, and emetine could prevent SASR-CoV-2 RNA synthesis. The novel vaccines such as mRNA1273 (Moderna), 3LNP-mRNAs (Pfizer/BioNTech), and ChAdOx1-S (University of Oxford/Astra Zeneca) targeting S protein have proven to be effective in combating the present pandemic. Further exploration of the potential of S protein and RdRp is crucial in fighting the present pandemic.

1. Introduction

Coronaviruses (CoVs) such as middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) are diverse classes of virus that infect animals and cause severe/mild respiratory diseases such as sore throat, runny nose, headache, chest pain, pink eye, fever, cough, tiredness, shortness of breath or difficulty of breathing, muscle aches, and chills [1], the MERS-CoV was discovered in 2012 [2], and SARS-CoV was discovered in 2003 [3–5]. The newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded, and positively-sensed virus. Genomic sequencing studies showed that SARS-CoV-2 and bat coronaviruses have similar (89%) DNA sequence. The CoVs are classified into *Alphacoronavirus, Betacoronavirus, and Gammacoronavirus*. The recently discovered SARS-CoV-2, together with the previously discovered MERS-CoV and SARS-CoV, are classified under *Betacoronavirus* – further classified into *Viruses; Riboviria; Orthornavirae; Pisuviricota; Pisoniviricetes; Nidovirales; Cornidovirineae; Coronaviridae; Orthocoronavirinae; Betacoronavirus; Embecovirus*. Also, *Embecovirus, Hibecovirus, Merbecovirus, Nobecovirus*, and *Sarbecovirus* are subgenera assigned to *Betacoronavirus* [4,5]. These viruses are highly pathogenic CoVs raising 21st century public health concern [6]. The disease (COVID-19) can be transmitted from human to human and animal to human by a droplet from coughing, sneezing, and direct

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contact [3,7]. Like other CoVs, studies have shown that SARS-CoV-2 is sensitive to ultraviolet rays (UV) and heat, and its functionality can be inhibited too using 70% ethanol, 75% ether, and chlorine [8].

Interaction of SARS-CoV-2 with angiotensin-converting enzyme receptor 2 (ACE2) promotes host entry [9], then a cytoplasmic release of RNA, leading to translation of SARS-CoV-2 ORFab and ORF1a into polyprotein 1b (ppab) and polyprotein 1a (pp1a) respectively, then cleavage of its polyprotein to non-structural protein is carried out by an enzyme encoded by ORF1a (transcriptional complex driving the formation of negative RNA strand and structural protein synthesis) [10]. Through discontinuous transcription, the viral genomic DNA is fragmented into genome materials encoding S, M (membrane), E (envelope), and N (nucleocapsid) protein. The translation of the genomic material encoding the S protein is carried out in the rough endoplasmic reticulum to synthesize S protein. Again, in the endoplasmic reticulum, assembly of viral protein and genomic RNA is carried out to form virion [4,5]. After the cellular invasion and pathogenic protein synthesis, the antigenic protein of SARS-CoV-2 binds to the central antiviral immunity called antigen-presenting cells. The major histocompatibility complex (MHC) presents the antigenic peptides followed by recognition by the cytotoxic T lymphocytes [11].

The RdRp and S protein are targets that could be explored to develop vaccines (some vaccines are currently developed encoding S protein) and repurpose existing antiviral drugs to fight the present pandemic. The S protein (relatively similar in both SARS-CoV-1 and SARS-CoV-2) allows SARS-CoV-2 to invade human cell after undergoing conformational changes leading from prefusion to post fusion conformation, resulting in binding and penetration into the human cell [9]. The RdRp of SARS-CoV-2 allows the virus to carry out RNA synthesis. A recent investigation by [12] has shown that the association of S protein with the ACE2 could be explored for drug and vaccine discoveries. Reported studies by [13] have shown that some of the investigated antiviral drugs such as Emetine (developed to inhibit RdRp) and umifenovir (developed to target viral entry) are proved to be safe and effective for the treatment of some viral infections, and they could be repurposed to target S protein and RdRp of SARS-CoV-2. To date, pharmaceutical companies and government are in the race of researching for effective drugs and vaccine development for COVID-19, and the World Health Organization (WHO) and many countries have encouraged the search for treatments to defeat the current pandemic [8]. However, this study reviewed research that is done on S protein and RdRp, towards vaccine, drug repurposing, and therapeutic development.

2. The role of S protein and RdRp in host infection

The S protein is the virulent target that mediates viral entry into the host and infection **(**Fig. 1**).** This protein is a trimeric and transmembrane protein present in human coronaviruses, human immune deficiency virus (HIV), influenza virus, paramyxovirus, and Ebola virus. The virulent protein mediates attachment to the cell membrane, recognition of ACE2 receptor, and fusion during infection [13,14]. Previous studies by [8,9] reported that the S protein trimer forms the basic unit by which S protein binds to the receptor. Recently, [15,16] highlighted that the S1 (mediating ACE2 recognition) and S2 (mediating fusion and entry) are division assigned to S protein (a glycosylated polypeptide existing in closed prefusion conformation), each playing a crucial role in SARS-CoV-2 infection. The S1 with the receptor-binding domain (RBD) participates in an interaction with the ACE2 receptor. While the S2 containing the HR domain (divided into HR1 and HR2) participates in the viral fusion [17]. An investigation by [18]revealed that the RdRp mediates the formation of replication machinery in the genome of SARS-CoV-2 by associating with replication factors. The elongation of the RNA strand is initiated and directed by RdRp through the addition of nucleotides. The RdRp using nucleotide analogue also catalyzes the halt of RNA elongation by inserting them into the new RNA chain that is being synthesized. The *de novo* (use of nucleotide by RdRp for RNA synthesis without the need of primers) and primer dependent synthesis (use of primers by RdRp to synthesize RNA by relying on short oligonucleotides) are the two modes of RNA synthesis used by SARS-CoV-2 [19]. Therefore, a better understanding of RdRp and S protein in the mediation of infection could lead to the development of novel vaccines and drugs for COVID-19.

3. SARS-CoV-2-S protein structure

The S protein of coronaviruses has a size of 180–200 kDa [12,13] and a total length of 1,273 amino acids (in which signal peptide located in the N-terminus comprises of amino acids 1 to 13, S1 subunit comprises 14–685 amino acids, and 686–1,273 amino acids make up the S2 subunit) [16]. The S1 subunit is divided into domains such as the N-terminal domain (comprising of 14–305 amino acid residues) and RBD (with 319–541 amino acid residues); while within the S2 subunit, there are domains such as fusion peptides domain (comprising of 788–806 amino acid residues), heptapeptide repeated sequence 1 domain (with 912–984 amino residues), heptapeptide repeated sequence 2 domain (comprising of 1,163–1,213 amino acid residues), a transmembrane domain of 1,213–1,237 amino acid residues, and a cytoplasmic domain which starts with 1,237 amino acid residues and ends up with 1,273 residues [20]. Also, the 3D Receptor Binding Domain (RBD) of SARS-CoV-2 (located in the S1 subunit) has a size of ~ 30 kDa. Previous studies by [21] revealed that the S protein architecture consists of the extracellular domain localized in the N terminal, transmembrane domain, and a metastable and prefusion stage intracellular domain segment, localized in the C-terminal. Also, a report from [22] highlighted that a crown like a halo adjoining the SARS-CoV-2 particle is formed by the trimers of the S protein. In an investigation by [23], the viral interaction with a host receptor could lead to structural rearrangement of the S protein which mediates cell membrane fusion by SARS-CoV-2. Even though there is a mutation in the S protein of SARS-CoV-2, but there still exists an interaction between RBD of S protein and ACE2; this indicates that S protein is a target to prevents viral entry [24].

The S protein of SARS-CoV-2 is highly glycosylated, the 22 N-glycosites and 2 O-glycosites per monomer are glycosites found in the trimeric structure of the S protein, where the RBD region has the 2 O-glycosites and 2 N-glycosites, and the N-glycosites (N122 and N343) are conserved. Even though glycosylation is specific to cell, its role in host protein interaction and mediation of infection in the epithelial airways is not fully understood. However, other studies reveal that the coated polysaccharide (localized on S proteins) helps the virus to avoid the immune system.

Cryo-electron microscopy (Cryo-EM) revealed the trimeric structure of S protein, its functions, together with the open and closed conformation of the RBD [8,25]. The S protein of CoVs exists as an inactive form precursor in its native state [17,26]. Also, the S protein is cleaved by a protease enzyme into S1 and S2 during infection [27], which is essential in the activation of the domain responsible for fusion [28]. The cleavage of S protein into S1 and S2 is done through the action of cellular protease using TMPRSS2 serine protease as a primer [29]. Recently, Cryo-EM studies by [26] revealed that a breath of S1 domain was observed (using cryoSPARC v2) after a hinge-like movement of the RBD, which is attributed to the poor resolution of S1 domain in comparison to S2 domain, the observation of the same features during the structural characterization of MERS-CoV and SARS-CoV have shown that SARS-CoV-2-S protein has the same mechanism of triggering infection with that of MERS-CoV and SARS-CoV. However, [26] pointed that there is a difference in the structure of the

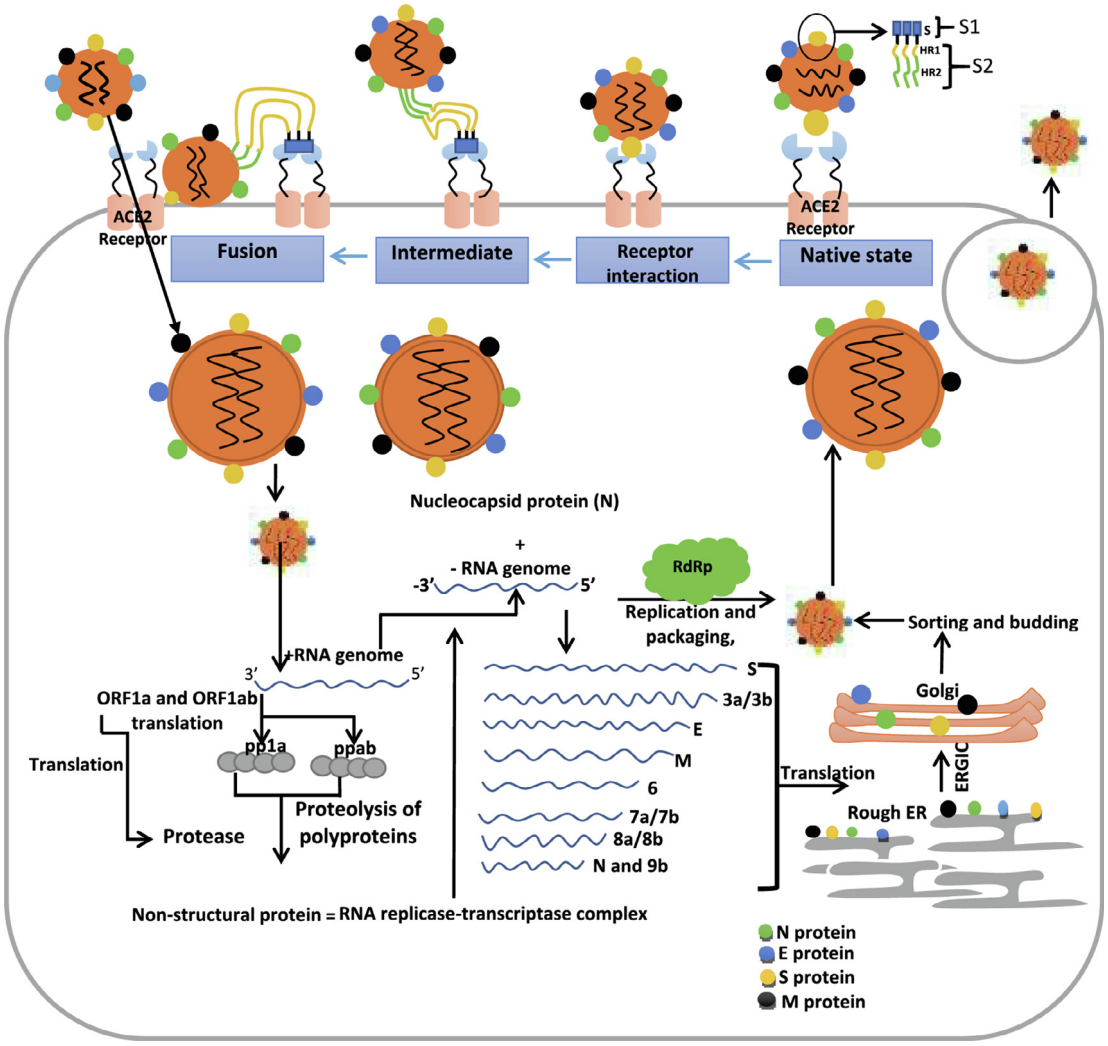

Fig. 1. An overview of the role of S protein and RdRp of SARS-CoV-2 in host infection.

RBD of SARS-CoV-2 and SARS-CoV, in which the position of the RBD of SARS-CoV-2 is in the down conformation, which forms an angle with a cavity, and that of SARS-CoV is opposite to the N-terminal of the neighbouring promoter which is packed in the down conformation. Both SARS-CoV-2 and SARS-CoV can bind to ACE2 receptor (as investigated using surface plasmon resonance) with different affinities, the binding affinity of SARS-CoV-2 (~15 nM) is higher than that of SARS-CoV, which accounts for its easy transmission from human to human [26]. Furthermore, [26] highlighted that high-resolution CryoEM revealed the formation of the complex by the ectodomain of SARS-CoV-2 with the human host ACE-2 receptor, which is the same as the complex formed by the previously discovered SARS-CoV. Reported studies by [8,18] investigated that the S protein undergoes structural rearrangement before fusion with the ACE2 receptor. The rearrangement is turned on by the S1 domain binding to the ACE2 receptor, followed by the destabilization of the prefusion trimers; this leads to the formation of post-fusion conformation that is highly stable. Then upon passage of the RBD through a hinge-like movement, the ACE-2 receptor can either be accessible or inaccessible. No previous studies have investigated the design of new viral entry inhibitors based on the understanding of hairpin structure trimers. Little is known about exploring the RBD of the S protein for the development of monoclonal antibodies for SARS-CoV-2.

4. Structure of RdRp

The viral genome encodes RdRp that mediates replication and gene transcription in association with transcription factors. The folding of RdRP appears to be a right-handed thumb complete with palm and fingers domain. The catalytic motifs (five of seven) are localized in the palm domain, which are highly conserved, while the F and G catalytic motifs are localized in the finger's domain [10,20,21]. Studies by [30] revealed that the catalytic function of RdRp's are mediated by RdRP core and related motifs. Therefore, no single studies have explored RdRp core and related motifs for therapeutic development. All RdRp's have the same mechanism of action even though the substrate requirement differs. The structure of RdRp consists of the nsp7-nsp8 heterodimer, nsp8 subunit, and nsp12 core catalytic unit [31]. Interestingly, structural similarities exist among the RdRp of SARS-CoV-2 and SARS-CoV. Therefore, repurposing drugs that target RdRp of SARS-CoV can be useful in fighting the SARS-CoV-2 pandemic. Previous investigation by [32] disclosed that the b-hairpin nidovirus-specific extension domain is localized in the nsp12 N-terminal. The palm subdomain and nidovirus RdRp associated nucleotidyl transferase domain (NiRAN) sandwiches the b-hairpin, this configuration is not present in the structure of SARS-CoV-2 RdRp. The nsp12 C terminal catalytic domain is connected to NiRAN via interface subdomain [33].

The SARS-coV-2 RdRp active site forms A to G conserved catalytic motifs, in which the palm domain carries the A to E motifs, while F to G motifs are localized in the finger subdomain, the DX2-4D (with conserved aspartic acid) catalytic motif is housed in the catalytic motif A. [34], the hinge that mediates conformational arrangement in association with an RNA template and substrate binding is called flexible loop, which is located in Motif B [35], the catalytic motif SDD is located in the C motif, which plays a crucial role in iron-binding. Recently, the investigation of the RdRp structure revealed that the D760 and D761 are involved in magnesium iron coordination during catalysis [36]. The regulation of catalytic activity is mediated by the conserved catalytic motif which is in the SDD region. The interaction of phosphate from incoming NTP is mediated by the F motif. The G motif mediates interaction with the template strand and directs the achievement of the catalytic site by the RNA template [31].

Recent report by [37] revealed the *in silico* binding of some clinically approved drugs (ribavirin, tenofovir, hydroxychloroquine, sofosbuvir, remdesivir, galidesivir, cefuroxime, and favipiravir) to RdRp, using a dynamics simulations, docking, and molecular modelling. Investigation by [38] using a computational method revealed that the protein (RdRp) is a potential target for the repurposing of drugs that are either in the market or under clinical trial. Their studies showed that some drugs could bind to RdRp and effectively terminate its replication. Moreover, the computational methods for the identification of new possible drugs need to be validated *in vitro* (based on re-docking approaches). Furthermore, other computational studies investigate the potential of some antivirals and natural compounds in the inhibition of SARS-CoV-2-RdRp, where they found that adefovir, zanamivir, and adefovir antivirals are good potential candidates of RdRP inhibition, while natural compounds such as piperine, demethoxycurcumin, and curcumin could potentially bind to RdRp with low affinity [33,35–38]. These computational studies need to be considered with caution. Indeed, recent studies proved that remdesivir is not efficient as initially retained [32]. There has been little research in the investigation of the mechanism of RdRp inhibition by remdesivir, and this can be a new area of research [39].

5. Drugs repositioned to target SARS-CoV-2-S protein and RdRp

Many efforts are ongoing by several research groups of scientists to develop effective therapeutic interventions against the SARS-CoV-2 since the discovery of the virus in late December 2019. Previous medicinal chemistry studies on COVs have accelerated these efforts [27,28]. Despite the diverse nature of CoV viruses, their genomic fundamentals are similar and thus essential for the identification of therapeutic targets [40]. Genetic sequencing has revealed that both SARS-CoV-2 and SARS-CoV belong to the same family of single-stranded enveloped RNA viruses [37,38]. Owing to the many similarities between SARS-CoV, MERS-CoV, and SARS-CoV-2, it is only rational to try drugs that have shown some level of activity previously on SARS-CoV and MERS-CoV [41]. Key enzymes responsible for virulence, attachment to host cells, and replication are significant targets for developing new drugs [30,31]. It has been shown that molecules that could inhibit the interaction between SARS-CoV-2 S protein and ACE2 receptor and other key viral enzymes essential for RNA synthesis and replication such as RdRp will serve as valuable targets in developing treatments for the novel virus [6,32].

As for developing drugs for novel coronaviruses, scientists employ at least three different strategies [33,42]. The first is to randomly test broad-spectrum antiviral agents on the novel pathogen. The second is the repurposing or repositioning of existing drugs meant for other therapeutic purposes and lastly is to develop drugs from scratch using available genomic information and pathological data of known coronaviruses [33,35,43]. With each method having its pros and cons, the combination of the three approaches is often utilized by scientists during CoVs outbreaks to identify potential drug candidates [40]. Different classes of drug agents that have displayed some level of potentials *in silico*, *in vitro*, or clinically against the novel coronavirus will be examined. Some of the drugs described have activity against other virus families or have already been used clinically against other viral pathogens, indicating potential broad-spectrum applications. These drugs can further be explored by other researchers owing to the potentials exhibited through prior studies.

5.1. Chloroquine

Drug repositioning has been initiated in recent years; drugs proven to be harmless with well-known optimal dosage and pharmacokinetics are important candidates for drug repurposing towards fighting the present pandemic [44]. Chloroquine synthesis was carried out in 1943, with the potential of treating malaria and rheumatoid arthritis. In 1955, hydroxychloroquine was developed and became a better candidate in place of chloroquine. The DNA interaction and heme polymerization inhibition are thought to be the mechanism of action of chloroquine and hydroxychloroquine [45]. The synthesis of hydroxychloroquine was done from chloroquine by introducing a hydroxyl group into a chloroquine structure, which is less toxic and safer than chloroquine [46]. Recently, [47] investigated the effect of chloroquine on primate cells infected with SARS-CoV. The effect of the drug was examined after and before infection with the virus (SARS-CoV-2), suggesting the possibility of both prophylactic and therapeutic potential. The terminal glycosylation of the ACE-2 receptor could be possibly terminated by chloroquine, which could possibly be the means of altering the viral entry. The elevation of endosomal pH by chloroquine could possibly contribute to affecting the growth of SARS-CoV. Recently, [47] investigated the potential of chloroquine to alter the replication of SARS by an *in vitro* study using indirect immunofluorescence. Their studies found that 10 μM of chloroquine could inhibit SARS-CoV replication. A recent report from [48] revealed the comparison of the effectiveness of chloroquine to hydroxychloroquine, with chloroquine being a more possible inhibitor of SARS-CoV than hydroxychloroquine *in vitro* in a Vero cell model. In contrast, the effectiveness of chloroquine in the inhibition of SARS-CoV-2 is still being debated. Recent studies by [49] reported that Vero cells expressing engineered TMPRSS2 (the protease enzyme involved in the activation of SARS-CoV-2 entry into the lung cells) makes the virus not sensitive to chloroquine. Hence, the target of chloroquine is the viral activation pathway, in which such pathway is inactive in lung cells. This accounts for its reduced ability to offer protection from the viral transmission.

5.2. Chlorpromazine

Chlorpromazine is a first-generation antipsychotic used for treating acute psychosis, schizophrenia, and bipolar disorder [50]. The idea to repurpose this drug to target SAR-CoV-2 stems from the observation relating a lower incidence of symptomatic COVID-19 disease in patients in psychiatric wards [51], leading to the hypothesis that psychotropic drugs administered to these patients may serve as prophylaxis for the SAR-CoV-2, granting immunity against virulent strains. Chlorpromazine has been recorded to have inhibitory activity against coronaviruses and could inhibit replication of MERS-CoV and SARS-CoV-1 [52,53] by targeting clathrin-dependent endocytosis which is essential for viral invasion, replication, and colonization [54]. The genomic similarity of SAR-CoV-2 to the two afore-mentioned coronaviruses makes it plausible to consider chlorpromazine repurposing for the potential treatment of COVID-19. One major feature of advantage is the distribution channel of the drug within the body. Studies show that the highest concentrations are found in the lungs [55] and saliva [56] than in blood and as COVID-19 primarily manifests

following initial lung infestation by the virus and mostly spreads due to high viral loads in body fluids like saliva, this biodistribution is important for reducing grave symptoms and limiting person-person transmission.

5.3. Hormone receptor antagonists

The attachment of SAR-CoV-2 spike protein with cells is accelerated by transmembrane protease serine 2 (TMPRSS2) through the androgen receptor signalling pathway [57] and this has been linked to variations in individual susceptibility, especially along the lines of age, as well as gendered disparity in mortality [58]. Compounds that inhibit androgen receptors are, therefore potentially beneficial for treating COVID-19. Malignant tumours are often characterized by high concentrations of androgen receptors and certain hormone receptor-amplified types of breast cancer tend to possess higher concentrations [59]. Tamoxifen is a drug used to treat hormone receptor-positive breast cancers as it prevents the binding of androgens to their receptor by binding there itself [60] and this makes it a potential drug candidate for the management of COVID-19. Toremifene is another drug candidate for SAR-CoV-2 treatment. It is a first-generation selective estrogen receptor modulator (SERM) and is currently used for the treatment of breast cancer [61]. While, unlike Tamoxifen, it does not appear to have direct receptor inhibitory properties, recent research has found that Toremifene has the potential to interact with SAR-CoV-2 spike glycoprotein in a manner that distorts the secondary structure, thus inhibiting its activity [62] and a related study found it capable of SARS-CoV-2 inhibition with an EC50 02.5 μM [63].

5.4. Remdesivir

Remdesivir (a broad-spectrum drug targeting viral replication) is currently under investigation towards repositioning. Gilead is the first pharmaceutical company that synthesized remdesivir for the treatment of Ebola. The drug is metabolized in its active form, which can lead to a reduction in the synthesis of viral RNA. The drug delayed chain cessation of nascent viral RNA as a means of terminating viral replication. The investigation of the antiviral activity of remdesivir using cell-based assay has revealed the activity of the drug on a rhesus monkey model infected with the Ebola virus [64]. Also, the possibility of *in vitro* inhibitory effect of remdesivir was observed in primary human epithelial cell culture infected with SARS-CoV-2. The drug has shown potential in the inhibition of human and zoonotic coronaviruses such as SARS-CoV, related bat coronaviruses, MERS-CoV, HCoVOC43, mouse hepatitis virus, coronavirus HKU5, HCoV-229E, and HCoV-NL63 [64]. An investigation has shown that intravenous treatment of rhesus monkey with 10 mg/kg of remdesivir (with an intracellular half-life of 14 h) can lead to 24 h presence of an active form of remdesivir (trisphosphate form) in the peripheral blood mononuclear cells and this could be applicable in SARS-CoV-2 infected animal species. According to [65], randomization of 1,062 patients (521 placebo and 541 remdesivir treated for 10 days), remdesivir treated patients recovered in 10 days, while placebo-treated group recovered in 15 days. In May 2020, the drug remdesivir was given emergency approval by the FDA. In the same month, two randomized clinical trials (one by Wang and Colleague and the other one by the National Institutes of Health-sponsored Adaptive COVID-19 Treatment Trial) took place to compare remdesivir with a placebo. The trial of Wang and his colleague with 237 patients failed to show any efficacy. While the trial of the institute recruited 1,063 patients (treated with remdesivir for 10 days) and observed a recovery period that is shorter by 4 days compared to the placebo-treated group. After the approval of remdesivir by the FDA, there have been considerable debates to ensure adequate, equitable, and affordable access to remdesivir as a result of the huge demand by patients and physicians [66]. However, a recent report by [67] highlighted against the use of remdesivir, as there is controversy in whether it improves survival and other outcomes (such as improving mortality rate, reduction in the need of ventilators etc.) in COVID-19 patients. This is a conditional recommendation against its use by WHO. Furthermore, recent news in BMJ [68] reported that the largest trial of remdesivir showed that it is not beneficial in reducing the disease course or mortality rate. The drug is too expensive to afford (costing $2,600 for 10 days intravenous infusion) and the disease is not rare. Therefore, many nations cannot afford the therapy. According to WHO, there is a need for the continued search for new antivirals, anti-SARS-CoV-2 monoclonal antibodies, and immune modulators.

5.5. Favipiravir

Favipiravir is another broad-spectrum antiviral that has demonstrated *in vitro* activity against many RNA viruses. It also acts as an inhibitor of RdRp [69], affecting the replication of a significant number of RNA viruses such as influenza A virus, flaviviruses, noroviruses, yellow fever virus, Ebola virus, and Lassa virus [70]. The drug inhibits replication moderately in Vero E6 cells when its efficacy against SARS-CoV-2 was tested [71]. Recently, Wang and colleagues highlighted the efficacy of favipiravir in reducing SARS-CoV-2 infection with a half-maximal effective concentration (EC50) of 61.88 mM, which similar to its EC_{50} against Ebola Virus Disease (67 mM)[72]. Overall, from clinical studies in COVID-19, when compared to lopinavir/ritonavir (LPV/RTV), favipiravir has shown a faster viral clearance rate and higher recovery rate when compared to umifenovir [72].

5.6. Emetine

The treatment of amebiasis can be done with Emetine (an FDA approved drug). This drug has the potential of causing toxicity of the heart, which restricted its utilization for the treatment of amebiasis. According to [73], some phytocompounds and antiviral drugs approved by FDA were tested for binding to RdRp, in which drugs such as Paritaprevir, Rilpinvirine, Simeprevir show affinity to RdRp with the binding energy ranging from −8.08 kcal/mol to −10.46 kcal/mol. Among the top phytocompounds, drug candidates that show affinity to RdRp are Oleanolic acid, 7,4-di-O-galloyltricetifavan, and Emetine, with a binding energy of −7.81 kcal/mol to −8.17 kcal/mol. The interaction between these drugs and RdRp is mediated by hydrogen and hydrophobic interaction. Therefore, investigation *in vitro* has shown the potential of Emetine to halt the replication of SARS-CoV-2, hCoV-OC43, MERS-CoV, hCoV-NL43, and MHV-A59 [74,75]. Upon the emergence of SARS-CoV-2 infection, the therapeutic potential of Emetine was examined *in vitro*, which shows that at cytotoxic concentration 50 (CC_{50}) of 1,603.8 nM and at 50 (EC_{50}) of 0.147 nM, Emetine has a therapeutic index of 10910.4. Treatment with Emetine could decrease the replication of virus by decreasing the synthesis of RNA and protein. Emetine could disrupt the binding of the eukaryotic translation initiation factor (a cap-binding protein needed for translation) with SARS-CoV-2 RNA in an investigation using chromatin immunoprecipitation assay [73,76].

5.7. Simeprevir

This drug is approved by FDA for the treatment of patients with Hepatitis C Virus (HCV) genotype 1, the drug is designed to inhibit the protease, and it is regarded as a second-generation macrocyclic inhibitor of protease. Simeprevir binds specifically to NS3 protease; this is an advantage over the first-generation protease inhibitor [77–80]. Interestingly, remdesivir could act synergistically with

simeprevir, and it could inhibit the activity of Mpro protease and RdRp based on evidence from molecular and biochemical characterization studies [81].

5.8. Lumacaftor

Lumacaftor is an orphan drug used in combination with ivacaftor to manage cystic fibrosis (CF) cases [82,83]. CF, an autosomal recessive disorder, is caused by genetic mutation of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein causes an autosomal recessive disorder known as cystic fibrosis [82,84]. Lumacaftor corrects mutation in the gene of CFTR protein by trafficking mutant protein to the plasma membrane in cystic fibrosis patients [84]. With a half-life of about 26 h in CF patients and reaching peak plasma concentrations 4 h after multiple oral ingestions, lumacaftor is well absorbed from the gastrointestinal tract with a 99% plasma-protein binding. It acts as a protein-folding chaperone, increasing the processing and trafficking of mature protein to the cell surface by improving F508del-CFTR conformational stability. Lumacaftor is poorly metabolized, with more than half (over 50%) of it excreted unchanged [85–87]. In search of therapeutics to curtail COVID-19, repositioning of existing drugs is a prime lead focus for the search. Lumacaftor has been reported to inhibit SARS-CoV-2 by targeting main protease ($3CL_{pro}$) and Nsp13 helicase [88–90]. It is also reported to have a high-affinity binding to the receptor-binding domain (RBD) of Spike (S) protein, thereby preventing SARS-CoV-2 interaction with angiotensin-converting enzyme-2 (ACE-2) [91,92]. In particular, lumacaftor forms hydrophobic bond to Leu455 and H-bonds to Lys417 and Gln493 – which are responsible for SARS-CoV-2 high affinity to ACE2 – thereby inhibiting S glycoprotein binding to ACE-2 [93].

5.8. Phytochemicals and natural products

The glycosylation process of the S protein could be inhibited by α-glucosidase 1 and α-glucosidase 2, resulting in the incorrect formation of glycoform, which will lead to ER-associated degradation, altering of protein–protein interaction, maturation inhibition. The unavailability of α-Glucosidase in the pneumocytes is evidence of its potential as an anti-SARS-CoV-2. An investigation using deep mutational scanning revealed that N343 glycosylation is important in the expression of RBD [91]. Also, evidence from computational simulation revealed that N-glycans (N165 and N234) in mediating the binding of S protein to ACE2 receptor [24]. Recent investigation revealed that monoterpenes such as 1,8-cineole and camphor, together with diterpenes (patchouli and carnosic) and triterpenes (ursolic acid), could potentially inhibit the entry and replication of SASR-CoV-2. The mechanisms used by these metabolites in the inhibition of SARS-CoV-2 infection are still unknown [94]. An alkaloid extracted from Stephania called Cepharanthine (used for snake bites, alopecia, and leukopenia) have shown to possessed antiviral efficacy [94,95]. The cancer and autoimmune drug called Thioguanine (with IC_{50} of 1.7 μM), after transformation to thioguanosine triphosphate, could potentially inhibit the GTP-binding protein (related to replication and DNA synthesis) and RdRp. Molecular docking investigation revealed that thioguanosine trisphosphate binds well with viral RdRp, but *in vitro* studies have shown that thioguanosine triphosphate did not exhibit the ability of RdRP inhibition. However, other studies revealed that thioguanosine triphosphate binds slowly and reversibly to PLpro of SARS-CoV-2 and SARS-CoV-2. Therefore, the potential of thioguanine in the inhibition of SARS-CoV-2 replication is a new area of research [96]. Until recently, there has been no reliable evidence that plant metabolite can alter the activity of S protein, there is a need for researchers to fully explore plant metabolites (Alkaloids, diterpneoid, anthraquinones, glycosides, flavonoids, Natural lupane triterpenoids, saponins, phenols, Tannins, gallic acid, flavonoids like quercetin and quercitrin, phenolics, Tannins, diterpenes, Saponins, triterpenes, terpenoids, sugar bearing compound, protein, thiols, etc. [96]) that can block the viral entry, especially from a plant with proof of antiviral properties for a potential chemical model for a cure against the novel SARS CoV-2 (Table 1).

6. Vaccines encoding spike protein

With the current outbreak of COVID-19, there is a strong need for the synthesis, distribution, and administration of the SARS-CoV-2 vaccines to safeguard public health. The scientific efforts to make this a reality has witnessed tremendous contributions from over 40 pharmaceutical companies and academic institutions globally. The development of not less than 321 vaccines has been recorded to be in progress as of October 2020, approximately more than twice as of April, indicating a significant advancement [97]. A total of 56 vaccines has undergone clinical trials (clinical trial phase 1 to 3) as of November 2020. However, the WHO reports a total of 280 vaccine candidates, with 97 COVID-19 vaccine candidates currently at different phases of clinical trials and 183 vaccine candidates at preclinical trials as of May 7, 2021 [98].

From preclinical studies to vaccine development against SARS-CoV-2, the antigenic target for coronavirus vaccines has become clear [99]. The S (host entry mediator) protein appears to be the target for a vast number of coronaviruses [29,100]. The viral genome is synthesized into the cytoplasm after entry [101]. Antibodies binding to the S protein serves as a building block for vaccine development [102]. The S protein-host-cell interface also serves as the main target of neutralizing antibodies and the focus of therapeutic and vaccine design. Vaccine development based on the S1 subunit of SARS-CoV-2 appears to be a promising approach [103]. The rigorous process of vaccine development takes a reasonable amount of effort and time before its approval for mass production, distribution, and administration. The availability of information on existing vaccine candidates in addition to the animal models from SARS and MERS expedited the regulatory processes owing to the inordinate and urgent need for efficient vaccines throughout the world. The protective ability of the vaccine is dependent upon the vaccine target and platform. In the last decade, there has been a significant evolution in the area of vaccine technology [104]. Several platform technologies (Table 2) including RNA replicons, plasmid-based DNA vaccines, subunit vaccines, live-attenuated vaccines, inactivated viral vaccines, killed whole virus vaccines, and the virus-like particle has been produced to provide immunity against diseases [45].

6.1. Oxford/AstraZeneca vaccine

One of the most prominent vaccines developed against COVID-19 is the chimpanzee adenovirus vectored vaccine called ChAdOx1 nCoV-19. The ChAdOx1 nCoV-19 (encoding spike protein) triggers humoral and cell-mediated response. The T helper cell is the agent that triggers this response; this is from IgG sub subclass profiling and cytokine expression evidence. Induction of a balanced cellular and humoral immune response is experienced upon vaccination with ChAdOx1 nCoV-19 [105]. A clinical trial of the vaccine revealed the vaccine was 62 to 90 percent effective, depending on the initial dosage. After phase 1 results supported a two-dose regimen, the trial protocols were adjusted two standard doses (SD/SD cohort) of approximately 5×10^{10} viral particles per dose administered 28 days apart, but a subset (LD/SD cohort) in one of the UK trials inadvertently received a half-dose of the vaccine (low dose) as the first dose before a change in dosage quantification [106]. One of the good features of this vaccine is that it can be stored, transported, and handled at normal refrigerated conditions of about 36 °F–46 °F for at least six months and administered within existing healthcare settings. The vaccine uses technology from an Oxford spinout company, Vaccitech. It deploys a

Table 1
Potential inhibitors of SARS-CoV-2 virus.

Drug	Class and point of inhibition	Antiviral effects exhibited in studies	Type of study	Reported MOA	Ref
Antibodies	Biologic; Cellular entry	SARS-CoV; SARS-CoV-2; MERS-CoV	*In vivo*	Neutralizes viruses by preventing the binding of viral spike protein to ACE2 on host cells	[71,103,115,116]
Chloroquine	Antimalarial; Cellular entry	SARS-CoV; SARS-CoV-2; MERS-CoV	*In vitro/ In vivo*	RdRp and ACE2 cellular receptor	[117]
Hydroxychloroquine	Antimalarial; Cellular entry	SARS-CoV; SARS-CoV-2; MERS-CoV	*In vitro/ In vivo*	RdRp inhibitor also targets endosomes and cause pH elevation	[70]
Remdesivir	Antiviral; Replication	SARS-CoV; SARS-CoV-2; MERS-CoV; EVD,	*In vitro/ In vivo*	Binds to RdRp which affects RNA production and ultimately putting a halt to viral replication	[118,119]
Favipiravir	Antiviral; Replication	SARS-CoV; SARS-CoV-2; MERS-CoV; EVD, Norovirus;	*In vitro/ In vivo*	RdRp Inhibitor	[70]
Chlorpromazine	Anti-psychotic; Viral entry	SARS-CoV; SARS-CoV-2; MERS-CoV	*In vivo/ in vitro*	Inhibition of clathrin-mediated endocytosis	[120]
Curcumin	Natural compound; Replication	SARS-CoV-2	*In silico*	Acts by interfering with vital steps in replication cycles such as viral attachment and genome replication	[121,122]
Emodin	Natural compound; Cellular entry			Hinders the interaction of SARS-CoV S protein with ACE2 which is essential for entry into the host cell	[70]
Theaflavin	Natural compound; Replication	SARS-CoV; MERS-CoV; SARS-CoV-2	*In silico/ In vitro*	May inhibit RdRp	[123]
Emetine	Natural compound; Replication	SARS-CoV-2; Zika virus; EBOV; Dengue virus; Human CMV	*In vitro/ In vivo*	Acts through viral RdRp inhibition	[41]
Simeprevir	Antiviral; Cellular entry	MERS-CoV; SARS-CoV-2	*In silico*	Binds RDB with high affinity and prevent ACE2 interaction	[93]
Hormone receptor antagonists	Anti-cancer; Cellular entry	SARS-CoV-2		Interaction with S protein and distort it secondary structure	
Lumacaftor	CFTR corrector; Cellular entry	SARS-CoV-2	*In silico*	Attaches to the RBD of CoV with high affinity and prevent ACE2 interaction	[93]
Phytochemicals and natural products	Natural compounds; Cellular entry	SARS-CoV-2, SARS-CoV, MERS-CoV	*In silico*	Altering the interaction of ACE2 receptor with S protein	[96]

replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (Adenovirus) that causes infections in chimpanzees. It contains the genetic materials of the spike protein. After vaccination, the cells produce the spike protein, stimulating the immune system to attack the SARS-CoV-2 virus [107]. Serious adverse events were evaluated in ChAdOx1 nCoV-19 recipients and control recipients. No serious adverse events or deaths that were treatment associated occurred in ChAdOx1 nCoV-19 recipients [106].

6.2. Pfizer/BioNTech vaccine

Another promising COVID-19 vaccine of much notable attention is the Pfizer-BioNTech's vaccine which was sent to the FDA for possible Emergency Use Authorization (EUA) on November and was authorized on December 11, 2020. It is an mRNA vaccine that codes for the virus's spike protein and is encapsulated in a lipid nanoparticle. Once injected, the cells churn out the spike protein, triggering the body's immune system to recognize the virus. In phase 3 trials, it demonstrated 95% efficacy. One of the major setbacks of the Pfizer-BioNTech vaccine is that it requires a cryo-storage of about −94 °F, which requires specialized freezers and therefore can affect the distribution chain [107].

6.3. Moderna vaccine

The vaccine (mRNA 1273) targeting spike protein developed by Moderna is also among the most promising vaccines. The mRNA 1273 vaccine contains RNA that codes for S protein. After its injection into the human system, the RNA migrates to cells and get translated to S protein; any cell containing the cell protein is targeted by the antibodies specific for S protein. The vaccine has good features of prompt modification of the encoded immunogen and quick manufacturing process [108]. Vaccine derived from RNA is safe and immunogenic from clinical trial evidence [78,79]. The United States is the first place where the clinical trial phase 1 of mRNA1273 (novel lipid nanoparticle encapsulated mRNA-based vaccine) vaccine took place in March 2020. The vaccine encodes the S protein with propitious production [109]. The clinical trial of the recently developed mRNA1273 in a mouse model has shown neutralizing antibody induction with promising protection against the current pandemic. Therefore, the vaccine can prevent the infection of lower and upper airways in non-human primates [110]. According to [111], the clinical trial phase 1 of mRNA1273 using three doses of the vaccine (25 μg, 100 μg, or 250 μg), where each dose was tested on 15 adults (aged between 18 and 55) for 28 days apart, after the first immunization, antibody level elevated, and after the second immunization, neutralizing activity in the serum were detected. But there are some adverse effects (chills, headache, pain associated with the location of injection, fatigue, myalgia) detected in most of the participants (half), but the mRNA1273 induced immunity in all adults that participated. Also, [112] investigates the immunogenicity and safety of the mRNA1273 vaccine and found that the effect can range from mild to severe, which is mostly after the second dose treatment.

6.4. Johnson and Johnson's vaccine

A biopharma called Johnson and Johnson's is involved too in the COVID-19 vaccine project. The vaccine is designed with a DNA encoding S protein, the DNA is inserted into Adenovirus (virus causing flu-like symptoms), as the vaccine was made with a DNA, it can be stored for up to 3 months at 2 °C - 8 °C, this is because DNA is more stable than RNA. The S protein produced by the cell migrate outside the cell

Table 2
Some of the recently developed vaccines for COVID-19.

Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	No. of doses	Schedule	Route of administration	Developers	Phase
IV	Inactivated virus	CoronaVac; SARS-CoV-2 vaccine (inactivated)	2	Day 0 + 14	IM	Sinovac Research and Development Co., Ltd	Phase 4
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co., + Wuhan Institute of Biological Products	Phase 3
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co., + Beijing Institute of Biological Products	Phase 3
VVnr	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222) (Covishield)	1–2	Day 0 + 28	IM	AstraZeneca + University of Oxford	Phase 4
			1–2	Day 0 + 28	IN	University of Oxford	Phase 1
VVnr	Viral vector (Non-replicating)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	1	Day 0	IM	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 3
VVnr	Viral vector (Non-replicating)	Gam-COVID-Vac Adeno-based (rAd26-S + rAd5-S)	2	Day 0 + 21	IM	Gamaleya Research Institute; Health Ministry of the Russian Federation	Phase 3
VVnr	Viral vector (Non-replicating)	Ad26.COV2.S	1–2	Day 0 or Day 0 + 56	IM	Janssen Pharmaceutical	Phase 3
PS	Protein subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)	2	Day 0 + 21	IM	Novavax	Phase 3
RNA	RNA based vaccine	mRNA −1273	2	Day 0 + 28	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4
RNA	RNA based vaccine	BNT162b2 (3 LNP-mRNAs), also known as “Comirnaty”	2	Day 0 + 21	IM	Pfizer/BioNTech + Fosun Pharma	Phase 4
PS	Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	2–3	Day 0 + 28 or Day 0 + 28 + 56	IM	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Phase 3
RNA	RNA based vaccine	CVnCoV Vaccine	2	Day 0 + 28	IM	CureVac AG	Phase 3
IV	Inactivated virus	SARS-CoV-2 vaccine (vero cells)	2	Day 0 + 28	IM	Institute of Medical Biology + Chinese Academy of Medical Sciences	Phase 3
IV	Inactivated virus	QazCovid-in® - COVID-19 inactivated vaccine	2	Day 0 + 21	IM	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase 3
DNA	DNA based vaccine	INO-4800 + electroporation	2	Day 0 + 28	ID	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	Phase 2/3
DNA	DNA based vaccine	AG0301-COVID19	2	Day 0 + 14	IM	AnGes + Takara Bio + Osaka University	Phase 2/3
DNA	DNA based vaccine	nCov vaccine	3	Day 0 + 28 + 56	ID	Zydus Cadila	Phase 3
DNA	DNA based vaccine	GX-19N	2	Day 0 + 28	IM	Genexine Consortium	Phase 1/2
IV	Inactivated virus	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	2	Day 0 + 14	IM	Bharat Biotech International Limited	Phase 3
PS	Protein subunit	KBP-COVID-19 (RBD-based)	2	Day 0 + 21	IM	Kentucky Bioprocessing Inc.	Phase 1/2
PS	Protein subunit	VAT00002: SARS-CoV-2 S protein with adjuvant	2	Day 0 + 21	IM	Sanofi Pasteur + GSK	Phase 3
RNA	RNA based vaccine	ARCT-021	ND	ND	IM	Arcturus Therapeutics	Phase 2
VLP	Virus like particle	RBD SARS-CoV-2 HBsAg VLP vaccine	2	Day 0 + 28	IM	Serum Institute of India + Accelagen Pty + SpyBiotech	Phase 1/2
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	1,2 or 3	ND	IM	Beijing Minhai Biotechnology Co.,	Phase 3
VVnr	Viral vector (Non-replicating)	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	1	Day 0	IM	ReiThera + Leukocare + Univercells	Phase 2/3
VVnr	Viral vector (Non-replicating)	VXA-CoV2-1 Ad5 adjuvanted Oral Vaccine platform	2	Day 0 + 28	Oral	Vaxart	Phase 1
VVnr	Viral vector (Non-replicating)	MVA-SARS-2-S	2	Day 0 + 28	IM	University of Munich (Ludwig-Maximilians)	Phase 1
PS	Protein subunit	SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native like Trimeric subunit Spike Protein vaccine)	2	Day 0 + 21	IM	Clover Biopharmaceuticals Inc./GSK/ Dynavax	Phase 2/3

Table 2 (*continued*)

Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	No. of doses	Schedule	Route of administration	Developers	Phase
PS	Protein subunit	COVAX-19® Recombinant spike protein + adjuvant	1	Day 0 + 21	IM	Vaxine Pty Ltd.	Phase 1
PS	Protein subunit	MVC-COV1901 (Spike-2P protein + adjuvant CpG 1018)	2	Day 0 + 28	IM	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 2
PS	Protein subunit	FINLAY-FR1 anti-SARS-CoV-2 Vaccine (RBD + adjuvant)	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	Phase 1/2
PS	Protein subunit	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant)	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	Phase 3
PS	Protein subunit	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	2	Day 0 + 21	IM	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology “Vector”	Phase 3
PS	Protein subunit	RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	2	Day 0 + 28	IM	West China Hospital + Sichuan University	Phase 2
PS	Protein subunit	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)	1	Day 0	SC	University Hospital Tuebingen	Phase 1
PS	Protein subunit	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	2	Day 0 + 28	IM	Vaxxinity	Phase 2/3
VVr	Viral vector (Replicating)	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	2	Day 0 + 28	IN	University of Hong Kong, Xiamen University, and Beijing Wantai Biological Pharmacy	Phase 2
RNA	RNA based vaccine	LNP-nCoVsaRNA	2	ND	IM	Imperial College London	Phase 1
RNA	RNA based vaccine	SARS-CoV-2 mRNA vaccine (ARCoV)	2	Day 0 + 14 orDay 0 + 28	IM	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	Phase 3
VLP	Virus like particle	Coronavirus-Like Particle COVID-19 (CoVLP)	2	Day 0 + 21	IM	Medicago Inc.	Phase 2/3
VVr + APC	Viral vector (Replicating) + APC	COVID-19/aAPC vaccine. The COVID-19/aAPC vaccine is prepared by applying lentivirus modification with immune modulatory genes and the viral minigenes to the artificial antigen presenting cells (aAPCs).	3	Day 0 + 14 + 28	SC	Shenzhen Geno-Immune Medical Institute	Phase 1
VVnr + APC	Viral vector (Non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors expressing COVID-19 minigene SMENP and immune modulatory genes. CTLs are activated by LV-DC presenting COVID-19 specific antigens.	1	Day 0	SC & IV	Shenzhen Geno-Immune Medical Institute	Phase 1/2
PS	Protein subunit	AdimrSC-2f (recombinant RBD +/− Aluminium)	ND	ND	ND	Adimmune Corporation	Phase 1
DNA	DNA based vaccine	Covigenix VAX-001 - DNA vaccines + proteo-lipid vehicle (PLV) formulation	2	Day 0 + 14	IM	Entos Pharmaceuticals Inc.	Phase 1
DNA	DNA based vaccine	CORVax - Spike (S) Protein Plasmid DNA Vaccine	2	Day 0 + 14	ID	Providence Health & Services	Phase 1
RNA	RNA based vaccine	ChulaCov19 mRNA vaccine	2	Day 0 + 21	IM	Chulalongkorn University	Phase 1
DNA	DNA based vaccine	bacTRL-Spike oral DNA vaccine	1	Day 0	Oral	Symvivo Corporation	Phase 1
VVnr	Viral vector (Non-replicating)	Human Adenovirus Type 5: hAd5 S + N bivalent vaccine (S-Fusion + N-ETSD). E2b- Deleted Adeno.	1–2	Day 0 + 21	SC Oral, or SL	ImmunityBio, Inc.	Phase 1/2
VVnr	Viral vector (Non-replicating)	COH04S1 (MVA-SARS-2-S) - Modified vaccinia ankara (sMVA) platform + synthetic SARS-CoV-2	1–2	Day 0 + 28	IM	City of Hope Medical Center + National Cancer Institute	Phase 1
VVr	Viral vector (Replicating)	rVSV-SARS-CoV-2-S Vaccine	1	Day 0	IM	Israel Institute for Biological Research	Phase 1/2
VVr + APC	Viral vector (Replicating) + APC	Dendritic cell vaccine AV-COVID-19. A vaccine consisting of autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	1	Day 0	IM	Aivita Biomedical, Inc., National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	Phase 1/2

(*continued on next page*)

Table 2 (*continued*)

Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	No. of doses	Schedule	Route of administration	Developers	Phase
LAV	Live attenuated virus	COVI-VAC	1–2	Day 0 or Day 0 + 28	IN	Codagenix/Serum Institute of India	Phase 1
PS	Protein subunit	CIGB-669 (RBD + AgnHB)	3	Day 0 + 14 + 28 or Day 0 + 28 + 56	IN	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 1/2
PS	Protein subunit	CIGB-66 (RBD + aluminium hydroxide)	3	Day 0 + 14 + 28 or Day 0 + 28 + 56	IM	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 3
IV	Inactivated Virus	VLA2001	2	Day 0 + 21	IM	Valneva, National Institute for Health Research, United Kingdom	Phase 1/2
PS	Protein subunit	BECOV2	2	Day 0 + 28	IM	Biological E. Limited	Phase 1/2
VVr	Viral vector (Replicating)	AdCLD-CoV19 (adenovirus vector)	1	Day 0	IM	Cellid Co., Ltd.	Phase 1/2
DNA	DNA based vaccine	GLS-5310	2	Day 0 + 56, or Day 0 + 84	ID	GeneOne Life Science, Inc.	Phase 1/2
PS	Protein subunit	Recombinant SARS-CoV-2 Spike protein, Aluminum adjuvanted	2	Day 0 + 21	IM	Nanogen Pharmaceutical Biotechnology	Phase 1/2
PS	Protein subunit	Recombinant protein vaccine S-268019 (using Baculovirus expression vector system)	2	Day 0 + 21	IM	Shionogi	Phase 1/2
VVnr	Viral vector (Non-replicating)	AdCOVID, Adenovirus-based platform expresses the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein	1–2	Day 0	IN	Altimmune, Inc.	Phase 1
PS	Protein subunit	SARS-CoV-2-RBD-Fc fusion protein	N/A	N/A	SC or IM	University Medical Center Groningen + Akston Biosciences Inc.	Phase 1/2
IV	Inactivated Virus	ERUCOV-VAC, inactivated virus	2	Day 0 + 21	IM	Erciyes University	Phase 2
PS	Protein subunit	COVAC-1 and COVAC-2 sub-unit vaccine (spike protein) + SWE adjuvant	2	Day 0 + 28	IM	University of Saskatchewan	Phase 1/2
PS	Protein subunit	GBP510, a recombinant surface protein vaccine with adjuvant AS03 (aluminium hydroxide)	2	Day 0 + 28	IM	SK Bioscience Co., Ltd. and CEPI	Phase 1/2
PS	Protein subunit	Razi Cov Pars, recombinant spike protein	3	Day 0 + 21 + 51	IM and IN	Razi Vaccine and Serum Research Institute	Phase 2
IV	Inactivated Virus	COVID-19 inactivated vaccine	2	Day 0 + 14	IM	Shifa Pharmed Industrial Co.,	Phase 2/3
PS	Protein subunit	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	2	Day 0 + 28	IM	The University of Queensland	Phase 1
DNA	DNA based vaccine	COVIGEN	2	Day 0 + 28	ID or IM	University of Sydney, Bionet Co., Ltd., Technovalia	Phase 1
DNA	DNA based vaccine	COVID-eVax, a candidate plasmid DNA vaccine of the Spike protein	N/A	N/A	IM or IM + electroporation	Takis + Rottapharm Biotech	Phase 1/2
VVnr	Viral vector (Non-replicating)	BBV154, Adenoviral vector COVID-19 vaccine	1	Day 0	IN	Bharat Biotech International Limited	Phase 1
RNA	RNA based vaccine	PTX-COVID19-B, mRNA vaccine	2	Day 0 + 28	IM	Providence Therapeutics	Phase 1
IV	Inactivated virus	Inactivated (NDV-based) chimeric vaccine with or without the adjuvant CpG 1018	2	Day 0 + 28	IM	The Government Pharmaceutical Organization (GPO); PATH; Dynavax	Phase 1/2
RNA	RNA based vaccine	CoV2 SAM (LNP) vaccine. A self-amplifying mRNA (SAM) lipid nanoparticle (LNP) platform + Spike antigen		Day 0 + 28	IM	GlaxoSmithKline	Phase 1
VLP	Virus like particle	VBI-2902a. An enveloped virus-like particle (eVLP) of SARS-CoV-2 spike (S) glycoprotein and aluminum phosphate adjuvant.	2	Day 0 + 28	IM	VBI Vaccines Inc.	Phase 1/2
PS	Protein subunit	SK SARS-CoV-2 recombinant surface antigen protein subunit (NBP2001) + adjuvanted with alum.	2	Day 0 + 28	IM	SK Bioscience Co., Ltd.	Phase 1
VVnr	Viral vector (Non-replicating)	Chimpanzee Adenovirus serotype 68 (ChAd) and self-amplifying mRNA (SAM) vectors expressing spike alone, or spike plus additional SARS-CoV-2 T cell epitopes.	2–3	Day 0 + 14 + 28 or Day 0 + 28 + 56 or Day 0 + 112	IM	Gritstone Oncology	Phase 1

Table 2 (*continued*)

Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	No. of doses	Schedule	Route of administration	Developers	Phase
RNA	RNA based vaccine	mRNA-1273.351. A lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2B.1.351 variant.	3	Day 0 or Day 0 + 28 or Day 56	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 2
PS	Protein subunit	SpFN (spike ferritin nanoparticle) uses spike proteins with a liposomal formulation QS21 (ALFQ) adjuvant.	2–3	Day 0 + 28 + 180	IM	Walter Reed Army Institute of Research (WRAIR)	Phase 1
PS	Protein subunit	EuCorVac-19; A spike protein using the recombinant protein technology and with an adjuvant.	2	Day 0 + 21	IM	POP Biotechnologies and EuBiologics Co.,Ltd	Phase 1/2
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	2	Day 0 + 14 +/− 21	IM	Organization of Defensive Innovation and Research	Phase 1
LAV	Live attenuated virus	MV-014–212, a live attenuated vaccine that expresses the spike (S) protein of SARS-CoV-2	3	Day 0 +/− 35	IN	Meissa Vaccines, Inc.	Phase 1
RNA	RNA based vaccine	MRT5500, an mRNA vaccine candidate	2	Day 0 + 21	IM	Sanofi Pasteur and Translate Bio	Phase 1/2
VLP	Virus like particle	SARS-CoV-2 VLP Vaccine	2	Day 0	SC	The Scientific and Technological Research Council of Turkey	Phase 1
PS	Protein subunit	ReCOV: Recombinant two-component spike and RBD protein COVID-19 vaccine (CHO cell).	2	Day 0 + 21	IM	Jiangsu Rec-Biotechnology	Phase 1
RNA	RNA based vaccine	DS-5670a, mRNA vaccine	2		IM	Daiichi Sankyo Co., Ltd.	Phase 1/2
IV	Inactivated Virus	Inactivated COVID-19 vaccine	2	Day 0 + 21	IM	Kocak Farma	Phase 1
VVnr	Viral vector (Non-replicating)	COVIVAC. Newcastle disease virus (NDV) expressing membrane-anchored pre-fusion-stabilized trimeric SARS-CoV-2 S protein +/− adjuvant CpG 1018	2	Day 0 + 28	IM	Institute of Vaccines and Medical Biologicals, Vietnam	Phase 1/2
VVnr	Viral vector (Non-replicating)	SC-Ad6-1, Adneviral vector vaccine	1–2	Day 0 +/− 21	IM	Tetherex Pharmaceuticals Corporation	Phase 1
VLP	Virus like particle	ABNCoV2 capsid virus-like particle (cVLP) +/− adjuvant MF59	2	Day 0 + 28	IM	Radboud University	Phase 1
PS	Protein subunit	Recombinant SARS-CoV-2 fusion protein vaccine (V-01)	2	Day 0 + 21	IM	Guangdong Provincial Center for Disease Control and Prevention/ Gaozhou Center for Disease Control and Prevention	Phase 2
RNA	RNA based vaccine	HDT-301: Self-replicating mRNA vaccine formulated as a lipid nanoparticle.	2	Day 0 + 28	IM	SENAI CIMATEC	Phase 1
IV	Inactivated Virus	Adjuvanted inactivated vaccine against SARS-CoV-2	2	Day 0 + 21	SC	The Scientific and Technological Research Council of Turkey (TÜBITAK)	Phase 1
RNA	RNA based vaccine	mRNA-1283	2	Day 0 + 28	IM	ModernaTX, Inc.	Phase 1
PS	Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO cell)	2	Day 0	IM	National Vaccine and Serum Institute, China	Phase 1/2
RNA	RNA based vaccine	EXG-5003; a temperature-sensitive self-replicating RNA vaccine expressing the receptor-binding domain of the SARS-CoV-2 spike protein.	1	Day 0	ID	Elixirgen Therapeutics, Inc.	Phase 1/2
IV	Inactivated Virus	Inactivated COVID-19 vaccine	2	Day 0 + 28	IM	KM Biologics Co., Ltd.	Phase 1/2

Source – WHO [98] (updated on April 1, 2021). ND: No Data; IM: Intramuscular; SC: Subcutaneous; ID: Intrademal; IN: Intranasal; SL: Sublingual; IV: Intravenous.

and stick to the cell surface. Upon vaccination, the vaccine breaks up SARS-CoV-2 S protein into fragments and released to the cell surface. The immune system then recognizes the protruding S protein and S protein fragment. Immunity is also provoked by the Adenovirus through switching the alarm system of the cell, which results in activation of nearby immune cells. Hence, resulting in the vaccine evoking a strong immunity against the S protein [113]. Clinical trial (phase 1 and 2) of Johnson and Johnson's vaccine in the US and Japan measures the immunogenicity, safety, reactogenicity upon intramuscular injection in 1 or 2 doses, while phase 3 trial of the vaccine measures the efficacy of the vaccine using 60,000 participants. The effect of the vaccine was assessed based on viral load, the occurrence of COVID-19, titres of neutralizing/binding antibodies, systemic and local adverse effects. However, the trial stopped as a result of illness observed in participants that are unexplained. During the phase 3 clinical trial, 30,000 participants were used to investigate the co-morbidities and molecular confirma-

tion. Interestingly, the US (100 million doses) and EU (400 million doses) have signed a contract for the production of Johnson and Johnson's vaccine [114].

7. Conclusion

COVID-19 pandemic has drawn great attention across multiple disciplines, including economics, finance, epidemiology, virology, and pharmacology, as a result of its widespread and life-threatening nature. The scientific efforts to provide an everlasting solution to this health menace have witnessed the production, prescription, and administration of a myriad of drugs and vaccines, some of which are still in the pipeline undergoing pharmacological studies to safeguard public health. The S protein essential in host interaction and entry and RdRP that mediates viral RNA synthesis are good molecular targets that researchers and scientists can explore to develop novel therapeutics. Currently, efforts have been made to develop mRNA1273 (Moderna), 3LNP-mRNAs (Pfizer/BioNTech), and ChAdOx1-S (University of Oxford/Astra Zeneca) vaccines targeting the S protein, but there is no novel drug developed to fight the present pandemic. The trial on the repurposing of existing antiviral drugs (such as chloroquine targeting spike protein and remdesivir targeting RdRP) is ongoing now. However, the safety of those drugs is still under investigation. Therefore, there is no known repurposed drug that is officially approved and recommended for use in fighting the present pandemic. Hence, a better understanding of the structure of S protein and RdRP toward novel therapeutic development and drug repurposing is highly recommended.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Yusuf Muhammed: Conceptualization, Project Administration, Software, Writing – Original Draft, Visualization, Supervision. **Abduljalal Yusuf Nadabo:** Writing – Original Draft, Visualization. **Mkpouto Pius:** Writing – Original Draft. **Bashiru Sani:** Writing – Original Draft. **Jafar Usman:** Writing – Original Draft. **Nasir Anka Garba:** Writing – Review & Editing. **Jaafaru Mohammed Sani:** Writing – Review & Editing. **Basit Opeyemi Olayanju:** Writing – Review & Editing. **Sunday Zeal Bala:** Writing – Original Draft. **Musa Garba Abdullahi:** Writing – Review & Editing. **Misbahu Sambo:** Writing – Review & Editing.

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