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PHARMACEUTICAL STRATEGIES TO COMBAT COVID-19

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ABSTRACT

With emergence of year 2020, the world has come up with a disaster in the form of SARS-CoV-2 or COVID-19 infection. Its outbreak forces the WHO to consider it as a pandemic disease, due to its worldwide transmission with crucial symptoms. Its impact was first noticed in Wuhan, China in December 2019 and hence term coined COVID-19 to this fatal disorder. The medical system is being put under pressure to control its spread and create more recovery. For primary measure to resolve the spread chain of infection the administration declared lockdown for discontinuity as social distancing is one of the weapons to fight against it. However, this pandemic harms the economy worldwide. But during this challenging scenario, the Pharmaceutical and Biotech industries around the world are having an opportunity to continue research in collaboration with renowned Universities research centers, government agencies for the novel discovery of vaccines based on innovative technologies to manage the treatment and to supply it globally. In this review article, based on the recent publication evidence, we fundamentally compile the challenges and opportunities facing by pharmaceutical industries for finding the vaccine and cure for pandemic COVID-19. This review anthologizes the various technologies based on which preventive and treatment measures would be prepared and providing a reference for future studies.

Keywords: COVID-19, Vaccine, Pharmaceutical companies, World health organization

INTRODUCTION

Coronaviruses, a large group of viruses mainly affect upper respiratory infections such as sinusitis, laryngitis, tracheitis causes pneumonia that ranges from sympathetic to fatal. SARS, MERS, and COVID-19 are the outcomes of lethal infection. SARS-CoV-2 causes the COVID-19 pandemic disorder, Centers for Disease Control and Prevention (CDC) confined that COVID-19 is a disease which passes to human from bats to pangolin and then to humans. SARS-CoV-2 structurally composed of a single-stranded RNA genome with four types of proteins such as S spike proteins, E, envelope proteins, M membrane proteins, and N nucleocapsid proteins with which they attach the human cells and infect them. RNA genome size varies from 26 to 32 kilobases [1-2]. The first coronavirus was discovered in the 1930s, from infectious bronchitis virus (IBV) in tamed chicken, in 1960s, human coronaviruses

were revealed [3]. Contagious COVID-19 transmitted from human to human by touch and droplet infection [4].

COVID-19 globally impacts the worldwide economy also apart from health hazards to the community, and in these pandemic condition pharmaceutical companies, medical emergency and various research centers come up with a challenging situation, contribute to developing a new therapy as well as treatment for the coronavirus [5]. All the research centers and pharmaceutical industries throughout the world involved in competition versus cooperation found out the vaccine against the COVID-19 [6]. They are under pressure to discover the new therapies which can eradicate this problem and at the same time, taking it as an opportunity to raise the stock economy of their respective countries and raised their research to the next level, where they can tackle this pandemic disease [7].

Industries developing vaccines are facing the challenges to conduct their preclinical studies fast, most of the research centers completing the Phase-II studies [8, 9]. Certain pharmaceutical companies such as Gilead and Eli Lilly steps forward in fighting COVID-19, which gives positive results in drug development and boost up the economy too. Most of the research centers followed the approaches working fast on preliminary safety and therapeutic efficacy of their investigational drugs and vaccines, to get the fast licensed sanction of the drug [10]. Recently Oxford University confirmed that they have completed their vaccine's preclinical studies on animals and within 3 months launch their vaccine in the market [11, 12].

Approaches for vaccine testing plays a crucial role in determining the effective dose and safety of the drug in the laboratory level using first in animals before use in human volunteers then stepwise procedures have followed in Phase II-III, where the non-infected, low-risk subject and COVID-19 positive case has compared with the placebo control group. Cases are strictly monitored to check the toxicity and immune resistance. To carry out the studies with human volunteers in this pandemic disease is a difficult and challenging task [13]. However, with fear of unknown threat and risk, researchers cannot stop their innovations and studies as previously also developed vaccines for certain pandemic infections had proved beneficial in reducing the mortality rate.

Different Vaccine Platforms

The DNA and RNA sequencing-based vaccines are in preparation because they easily translated into proteins by host cells and facilitate the exogenous cytokines which can enhance or direct the immune response. DNA and RNA sequences called immune stimulatory sequence can be potent adjuvants. Figure 1 shows the proportion of vaccines based on different platforms. Following are the list of the platforms on which the vaccine preparation based in Phase I trial studies:

- Nucleic acid (DNA or RNA) based (Moderna, mRNA-1273 preparing the mRNA principle-based vaccine)
- Viral vector (CanSino Biologics, adenovirus type 5 vector based on this)
- Virus-like particle involved in DNA replication (Shenzhen Geno-Immune Medical Institute, LV-SMENP) [14][15]

Firstly, virus S spike protein is a promising immunizing agent, as it involves the infection of human cells on the entry of the virus. US National Institute of Allergy and infectious diseases in collaboration with the US National Institute of Health has worked on the preparation of vaccines based on this mechanism [14].

Secondly, preclinical understanding with vaccine candidates for SARS and the Middle East respiratory syndrome (MERS) has elevated anxieties about aggravating lung disease, either directly or as a result of antibody-dependent augmentation. Such a contrary consequence may be allied with a type 2 helper T-cell (Th2) response. Hence, testing in an opposite animal model and demanding safety monitoring in clinical trials will be critical and it is too early to express good animal model, however, data and careful regulatory review will be needed to determine the safe and effective immune response [15].

Third, the potential duration of immunity is unknown; similarly, whether single-dose vaccines will confer immunity is uncertain.

Traditional Vaccine versus Pandemic Paradigm

The development of a vaccine is a protracted exorbitant task, spend many years to finally get the authorized product. To resolve the adverse reactions and improve the safety and efficacy of the vaccine,

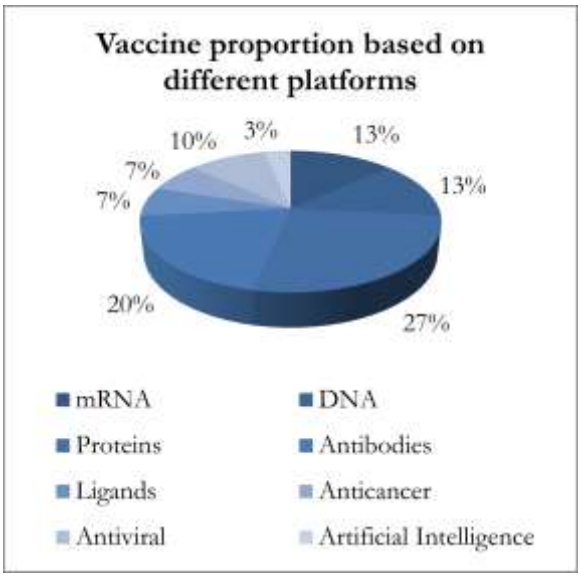

Fig 1. Proportion of vaccine developing based on different platforms

several statistical analyses have done based on manufacturing process facts.

Scrutinizing the facts disclose that as the COVID-19 outbreak arises in Wuhan, China, CEPI approached their associates working on a vaccine for Middle East Respiratory Syndrome, provided them financial assistance when the immunization process proceeded to begin after the introduction of the first gene sequence of COVID-19. Moderna vaccine development began their preclinical Phase I trial in March 16, another Nucleic acid-based vaccine started to begin from April [14][15]16]. Commercial large scale production, will begin after getting the facts about the safety and immunogenicity of the vaccine. The manufacturing process and technologies cost millions of dollars.

During pandemic situations conducting a clinical trial, testing is quite challenging. It is difficult to estimate the site and time of pandemic outbreak and preparation of vaccine batch for testing. Coincidentally on the production of multiple batches by the last of 2020, also can affect the regulatory authorities and financial assistance of the countries with trials, as this pathetic condition also occurs during the 2013-2016 outbreak of Ebola therapeutics[17]. Concurrent testing of several vaccines using the shared control group would help develop the effective vaccine, however, it is arithmetically complex.

Reviewed articles reveal that approaches have designed to provide manufacturing and financial support for vaccine development against COVID-19, for that many global stakeholders' steps forward and CEPI is one of such examples [16]. CEPI divided the vaccine production stage into certain classes such as;

- Exploratory were designing and planning of vaccine takes place,

- Preclinical where in vivo evaluation carries out or;
- Initiation of Phase I studies which demonstrates the safety and efficacy of the vaccine.

Ultimately Serologic and clinical studies will be established to check out the risk parameters and could form the keystone for impartial vaccine distribution systems globally. And if the COVID-19 outbreaks instantaneously epilogue before vaccines arrive, then also vaccine development should keep up so that they can be stocked and further trial for future perspectives if pandemic situation recurs [17].

Research framework of COVID-19 Vaccine

A COVID-19 vaccine is based on theoretical aspect. Several attempts are in progress for preclinical studies [18]. Around five hundred clinical studies across worldwide in all phases were registered with the World Health Organization Clinical Trial Registry, as of March 2020 [19]

For vaccine preparation, the SARS-Cov-2 structure is important, mainly its Spike protein 'S', as the vaccines are based on the hypothesis that they can change the structure of the virus, and make it ineffective in the human body and viable antigen could be present in the vaccine [20].

Around 70% private companies focus mainly on vaccine development and are involved in it. While the other 30% remaining projects are under the academics, government, and health organizations. Most of the research teams are working in collaboration with multinational pharmaceutical companies, as they are having less trial on this. Globally 40% of the world's active vaccine research is from the United States and Canada, 36% from Asian countries and China while 18% from Europe and Australia [21].

From the data surveyed in early March 2020, The Coalition for Epidemic Preparedness Innovations (CEPI) announced a US$2 billion financial assistant in a global partnership between the public, private, charitable, and civil society organizations to fasten the development of COVID 19 vaccines and its initiatives increased at a faster rate. As from the surveyed reports, it has been found that in April, the Canadian Government invested billion inventive funds for vaccine research, development, and clinical trials through the year 2022. 115 vaccine candidates were developed out of which 78 confirmed active while 37 are unsubstantiated. Of the 78 confirmed active, 73 projects are at the preclinical stage till April 2020 [22].

The director of the Vaccine & Immunotherapy Center at the Wistar Institute in Philadelphia and his group were already part of a project led by pharmaceutical company Inovio to develop a DNA-based vaccine for Middle East Respiratory Syndrome (MERS), which is caused by a coronavirus [23].

Table 1. Moldock score, Rerank score of top 10 antiviral compounds when docked with PDB 5DUS, 6W63, 3V3M with their H-bond values and interactions.

Vaccine and their innovator	Clinical Trial Phase	Country	Expected time duration	References
Ad5-nCoV (CanSino Biologics)	Phase II interventional trial for dosing and side effects (500)	China	March 2020 to December 2020	[28]
ChAdOx1 nCoV-19 (Oxford University)	Phase I-II, randomized, placebo-controlled, multiple sites (510)	United Kingdom	April 2020 to May 2021	[29]
BNT162 (a1, b1, b2, c2) (BioNTech, Fosun Pharma & Pfizer)	Phase I-II of four vaccines, dose-escalation, parallel cohorts (196)	Germany	April 2020 to May 2021	[30]
Sinovac Biotech vaccine	Phase I-II randomized, double-blinded, single-center, placebo-controlled (744)	China	April 2020 to December 2020	[31]
INO-4800 vaccine (Inovio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute)	Phase I-II (40)	United States, South Korea	April 2020 to November 2020	[32]
mRNA-1273 vaccine (Moderna, US National Institute of Allergy and Infectious Diseases)	Phase I (45)	United States	March 2020 to Spring-Summer 2021	[33]
aAPC vaccine (Shenzhen Geno-Immune Medical Institute)	Phase I (100)	China	March 2020 to 2023	[32]
LV-SMENP-DC vaccine (Shenzhen Geno-Immune Medical Institute)	Phase I (100)	China	March 2020 to 2023	[34]
Bac-TRL-Spike vaccine (Symvivo Corporation, University of British Columbia, Dalhousie University)	Phase I (84)	Canada	April 2020 to December 2021	[34]

Another vaccine designing technique involves an intramuscular injection of DNA along with the electric pulses applied to the site via small needles, this makes the cell membranes more permeable to the genetic material, thus treat the human cell by controlling the immune system [24].

Likewise, other Biotech companies like Moderna have prepared a new vaccine based on fatty nanoparticles fused with S Spike protein and cause structural changes in the coronavirus. Similarly, Imperial College London is designing a vaccine utilizing RNA as its genetic code, while Pennsylvania biotech company Inovio is utilizing the DNA strand to restore the immune riposte.

Johnson & Johnson and French pharmaceutical giant Sanofi both are working with the US Biomedical Advanced Research and Development Authority to develop vaccines. French Pharmaceutical has decided to react DNA from SARS-Cov-2 with DNA or RNA from another harmless virus [25], whereas Johnson &

Johnson has planned to block the activity of coronavirus and boost up the immune response, they are about to start their Phase II studies with human volunteers by September 2020 and the CEO of the company stated that they increase the amount of vaccine production sharply [26].

The University of Cambridge is associated with the DIOSynVax, a biotech company is making the use of computer modeling, with which they can change the virus structure to find frail spots in the SARS-CoV-2 DNA, and block the immune reactions, Jonathan Heeney, CEO of DIOSynVax considered it as a magic bullet [27].

Certain research organizations, such as Boston Children's Hospital, are working on some auxiliary substances which escalate the efficacy of vaccines.

Planned Clinical Phase I trials in 2020

Around 45-58% vaccine aspirant reaches the Phase I Clinical trial studies and further testing in human volunteers is critical due to lack of safety, effective dose, and financial support [35]. Assurance to first-in-human testing of a vaccine contender signifies a significant investment cost for vaccine inventors, valued to be around US$14 to US$25 million for an archetypal Phase I trial program, but possibly as much as US$70 million [34][36]. The present situation can be compared with vaccine development during the 2013-2016 Ebola virus epidemic outbreaks where only one vaccine out of 37 developed vaccines was succeeded to be licensed at a total cost and confirmed therapeutic effectiveness in Phase II trials with investment around US$1 billion [36, 37].

Non-specific vaccine

Nowadays, a trial has been done especially in the BCG vaccine, because certain vaccines can develop antibodies for other viral infections also for example in March 2020, Netherland runs a stochastic trial on BCG vaccine to combat Covid-19 and declared fewer cases using this vaccine but WHO nullify this theory in April 2020. Although Australia is seeking further randomized trials in 4170 healthcare workers [38].

Pharmaceutical companies involved in developing coronavirus drugs/vaccines

Following are the list of Pharmaceutical industries researching certain drugs which have the potency to combat COVID-19

1. Remdesivir: Biotech firm Gilead Sciences are doing experimental research on anti-viral drug Remdesivir. However countries like US, China, and Italy have used redeliver but does not receive approval, as remdesivir is not specific for treatment against SARS-CoV-2 but since it prevents RNA Polymerase enzyme where the virus replicates, therefore its use is continuous for the seriously ill patient as reported by NEJM, but its use as a primary treatment against SARS-CoV-2 is under discussion by WHO [39].

2. Favipiravir: Favipiravir is an antiviral drug manufactured by Fujifilm Toyama chemical, which is effective against the Japanese influenza virus and coronavirus, therefore Guardian, A Chinese Scientist in Wuhan and Shenzhen performs Clinical trial studies on it, however, the drug does not support to be a good choice against severe symptoms of COVID-19, although Shenzhen, Guangdong region which has licensed by The National Medical Products Administration of China continue clinical trials on human volunteers [39].

3. Chloroquine approved for emergency use by US FDA: The US Food and Drug Administration (FDA) approved chloroquine and

hydroxychloroquine for prophylactic use against COVID-19 and has been tested by different research organizations. The President of the United States, Donald Trump, had announced on 19 March that chloroquine and hydroxychloroquine/Plaquenil, the antimalarial drug has requested India to manufacture and supply them hydroxychloroquine. On 18 March 2020 journal Nature, recommended it to be effective against SARS-CoV-2 infection, as chloroquine increases endosomal pH and also involved in cellular uptake of SARS-CoV-2 which inhibits the sialic acid biosynthesis, as this inhibits the viral infection [40].

4. Actemra by Roche: China is continuing to conduct clinical trial studies in drug Actemra manufactured by Roche. Drug Actemra can prevent over expressions of the immune system, which was also reported as a reason behind the organ failure during SARS-CoV-2 infection. Clinical trial studies may be completed by july and it is expected to enroll around 188 COVID-19 patients [41].

5. Similarly, Drug Galidesivir, an antiviral drug from Biocryst's Pharma is a nucleoside RNA polymerase inhibitor, which inhibits virus replication, has shown remarkable benefits against other serious viral infections such as Ebola, Zika, Marburg, and Yellow fever. And the drug is in the advanced development stage against various species of viruses apart from coronaviruses such as flaviviruses filoviruses, paramyxoviruses, togaviruses, bunyaviruses, and arenaviruses [41].

6. Regeneron's REGN3048-3051 and Kevzara: National Institute of Allergy and Infectious Diseases (NIAID) sponsored a first-in-human clinical trial for a combination of neutralizing monoclonal antibodies REGN3048 and REGN3051 which was discovered by Regeneron. These antibodies are found to be effective against MERS coronavirus. Regeneron also merged with Sanofi and evaluated kevzara, a fully human monoclonal antibody, which is in Phase-II and III clinical trial studies with SARS-CoV-2 infection, it inhibits the interleukin pathway, which causes inflammatory reactions for lungs infection in COVID-19 patients [42].

7. SNG001 by Synairgen Research: The University of Southampton in collaboration with Synairgen Research discovered SNG001, a naturally occurring interferon-β inhaled drug, which was found to be effective against asthma, chronic obstructive pulmonary disease, and lower respiratory tract infection due to COVID-19 [42].

8. AmnioBoost by Lattice Biologics: Lattice Biologics developed an amniotic fluid concentrate, AmnioBoost which was known for its efficacy to reduce the inflammatory conditions caused by a coronavirus [42].

Following are the coronavirus vaccines in many phases of growth, across the world:

- *Entos Pharmaceuticals*: has worked on the Fusogenix DNA vaccine which has been prepared using the proteo-lipid vehicle which utilized multiple protein epitopes derived from SARS-COV-2 proteins, which will kindle an immune retort in the body to avert COVID-19 infection [42].
- *ChAdOx1 nCoV-19* by the University of Oxford: The University of Oxford in collaboration with the university's Jenner Institute developed ChAdOx1 nCoV-19, an adenovirus vaccine. They scheduled clinical trials for vaccines using 510 volunteers in the Thames Valley Region [43].
- Recently Oxford University in collaboration with *Astrazenecais* involved in research of the Plc vaccine where they have mixed genetic material of common cold, Adenovirus with SARS-Cov-2

virus, however, the prepared vaccine was found not so effective, but still, they are about to start the second phase clinical trial involving approx. 10,000 human volunteers of different age groups [42].

- *Altimmune*: The University of Alabama at Birmingham (UAB) in collaboration with Altimmune developed a single dose ADCOVID, intranasal vaccine, which is based on the same technology as NasoVax, influenza vaccine. They recently carried immunogenicity studies and will conduct Phase I clinical trial studies till October 2020 [43].
- *Airway Therapeutics*: The Airway Therapeutics company has demonstrated a research project on the COVID-19 vaccine with the Respiratory Diseases Branch of the National Institutes of Health to reconnoiter novel human recombinant drugs. AT-100 has shown effectiveness in preclinical studies to lessen swelling and contagion in the lungs and inhibit an immune overexpression against SARS-CoV-2 [44].
- *TZLS-501* by Tiziana Life Sciences: Tiziana Life Sciences develops TZLS-501, monoclonal antibody, and human anti-interleukin-6 receptor (IL-6R) against COVID-19, which reduces the echelons of IL-6 and reduces chronic lung inflammation [43].
- *OYA1* by OyaGen: OYA1 developed by OyaGen company was previously permitted as a trial-based anti-cancer drug but was unrestrained due to the dearth of effectiveness. But now, further researches are scheduled on the drug to determine the efficacy against SARS-CoV-2 infection [41].
- *INO-4800* by Inovio Pharmaceuticals and Beijing Advaccine Biotechnology: Inovio Pharmaceuticals has joined forces with Beijing Advaccine Biotechnology Company to conduct the expansion of INO-4800, as a new coronavirus vaccine. The vaccine growth was funded by a $9m grant from the Coalition for Epidemic Preparedness Innovations (CEPI). The firm has commenced the preclinical testing for clinical product manufacturing and also readied 3,000 doses for human clinical trials prearranged to be steered across the US, China, and South Korea. Consequences from the clinical trials are likely to be available in mid of September 2020. Once approved, then they will produce one million doses of the vaccine by the end of 2020 [41].
- *NP-120* (Ifenprodil) by Algernon Pharmaceuticals: Algernon Pharmaceuticals has developed Ifenprodil, glutamate receptor antagonist sold under the brand name Cerocal. It has demonstrated efficacy against H5N1 infection and can be effective against COVID-19 [41].
- *APN01* by University of British Columbia and APEIRON Biologics: The University of British Columbia has collaborated with APEIRON Biologics and developed APN01 for treating SARS. The research revealed that the ACE2 protein was the main receptor for the SARS virus and the clinical trial tests will signify the drug's efficacy against the protein. Data from the clinical trial will conduct further research [41].
- *Moderna and Vaccine Research Center*: Moderna and the Vaccine Research Center, a unit of the National Institute of Allergy and Infectious Diseases (NIAID), have collaborated and developed mRNA-1273, a vaccine against coronavirus. The vaccine targets the Spike (S) protein of the coronavirus. Phase I clinical trial studies has completed successfully and will enter the second phase in July [46].

- *Chinese CanSino Biologics Inc Vaccine*: This Company currently leading the race arise as a strong aspirant globally, they develop the vaccines using mutation of Ad5 virus, this genetically modifies the protein structure when injected in human body cell with which body not allowed the coronavirus to multiply and amplify the immune response and T-cell production inside the body. The prepared vaccine was tested successfully and safely in 108 human volunteers of the 18-60 age group. With this vaccine during trial antibodies develop within two weeks whereas 28 day's time period required for antibodies development, this created hope, further trials yet have to be carried soon [47].
- *Recombinant subunit vaccine* by Clover Biopharmaceuticals: Clover Biopharmaceuticals developed a recombinant subunit vaccine using its patented Trimer-Tag© technology, based on the trimeric S protein (S-Trimer), which is accountable for binding with the host cell and causes a viral infection. cGMP biomanufacturing capabilities are available and the company has collaboration with Galaxo Smith Kline to scale-up production when the vaccine is approved for efficacy [47].
- *ICMR-BBIL vaccine*: Indian Council of Medical Research in association with Bharat Biotech International Ltd in the Institute of Virology, Pune, India identified the coronavirus strain and working for vaccine development [47].
- *CytoDyn-leronlimab*: USFDA approved leronimab drug, a CCR5 antagonist examined by CytoDyn against SARS-CoV-2 infection.
- *BXT-25 by BIOXYTRAN*: BIOXYTRAN has developed BX-25, a lead drug candidate for Acute Respiratory Distress Syndrome (ARDS) treatment in last-stage patients infected with the coronavirus. The smaller size of the drug molecule helps in carrying oxygen effectively [45].
- *MERS CoV vaccines*: Novavax has been funded from CEPI to advance the development of the Middle East Respiratory Syndrome (MERS) vaccine in 2013. The candidate binds to the most important superficial S-protein and developed using recombinant nanoparticle vaccine technology. Human trials have planned to be conducted in 2020 [46].
- *Inovio Pharma's INO-4700*: in collaboration with GeneOne Life Science developed Cellectra® delivery device. The project has received a subvention from Bill and Melinda Gates Foundation [45].
- *Predictive Oncology*: Predictive Oncology designed vaccine in association with Invent BioTech.The company has signed an agreement with acquiring Soluble Therapeutics, to develop a vaccine based on HSCTM Technology.
- *Emergent BioSolutions*: Emergent BioSolutions developed polyclonal antibodies consequential from plasma, which enhances the immune response. Vaccines for Smallpox, Anthrax, Botulism are good examples that are based on the same technology [43].
- *CEL-SCI*: CEL-SCI developed immunotherapy against COVID-19 using its proprietary LEAPS peptide technology, which was based on the efficacy of coronavirus proteins to generate T-cell responses and reduce viral load. The technology utilizes immunotherapeutic which inhibits inflammation in the lungs during infection.
- *Pfizer BNTECH vaccine*: Pfizer in association with German company BNTECH prepared four candidates of vaccine, preclinical tests are recently going on in Germany and parts of the USA [47].

- *Takeda Pharmaceutical Company*: has developed polyclonal hyperimmune globulin (HIG) therapy against seriously ill patients. Treatment involved the induction of specific antibodies from plasma of recovered Covid-19 patients. Such antibodies originate immune response when inoculated into a new patient [48].
- *Heat Biologics*: Working on G96 protein, which triggered the host cell [48].
- *Mateon Therapeutics*: Mateon Therapeutics is working on artificial intelligence (AI) platforms. Similarly, researchers at the Hong Kong University of Science and Technology have recognized B-cell and T-cell epitopes, Tulane University identified a potential vaccine. All making attempts to amplify the immune response [49].
- *ImmunoPrecise Antibodies*: ImmunoPrecise Antibodies has planned a vaccine and therapeutic antibody program to develop a vaccine utilizing its B Cell Select™, DeepDisplay™ PolyTope mAb TherapyTM, and EVQLV's artificial intelligence platforms to progress therapeutic composites contrary to the coronavirus [49].
- *Serum Institute of India*: Serum Institute of India (SII) is an association with Codagenix, a US-based biopharmaceutical company developed a treatment for Covid-19 using a vaccine strain similar to the original virus. Research is currently in the pre-clinical testing phase, while human trials are prearranged to happen in imminent six calendar months. SII is anticipated to unveil the vaccine soon by 2022. By latest information, till June 2020, India is working fast for vaccine production and shocked everyone in the world with a good information to share that Glenmark launches Favipiravir, antiviral drug under the brand name "Fabiflu" for treatment of mild to moderate Covid-19 after receiving the approval from Drugs Controller General of India (DCGI) [41].
- *Southwest Research Institute*: Southwest Research Institute was using its simulated screening called Rhodium to recognize possible drug contenders against SARS-CoV-2 infection [41].
- *Zydus Cadila*: Zydus Cadila conducted the development of vaccines using two approaches:1) Using a DNA vaccine against M membrane protein of SARS-Cov-2; 2) a live-attenuated recombinant measles virus (rMV) vectored vaccine.
- *NanoViricides*: NanoViricides, a clinical-stage company, developing a treatment for nCoV-2019 using its nanoviricide® technology which is based on ligands attachment within the virus in the same manner as a cognate receptor and attack various sites of the virus [41].
- *Vir Biotechnology*: Vir Biotechnology, a clinical-stage immunology company researching monoclonal antibodies that can bind to the virus, which causes the infection and has done partnership with various companies such as WuXi Biologics to commercialize the antibodies, Alnylam Pharmaceuticals for siRNA and with Biogen for the cell line [49].

- *Anti-HIV drugs for coronavirus treatment*: Abbvie's HIV protease inhibitor, lopinavir is being considered along with ritonavir for the dealing of MERS and SARS coronaviruses. WHO has recommended the combination of Lopinavir/ritonavir in combination with ribavirin in the list of essential medicines. Cipla has also planned to continue research on its HIV drug LOPIMUNE, which is an amalgamation of protease inhibitors, Lopinavir and Ritonavir [41].
- *Janssen Pharmaceutical Companies*: A subsidiary of Johnson & Johnson, donated its PREZCOBIX® HIV medication (darunavir/cobicistat) for use in research activities intended at finding a treatment for COVID-19. Darunavir has found to have anti-viral activity against SARS-CoV-2 infection. Moreover, Janssen has aligned with the Biomedical Advanced Research and Development Authority (BARDA) to accelerate the progress of a COVID-19 treatment [49].
- *Convalescent plasma therapy*: On March 24, the US FDA announced it would allow access to "convalescent plasma" for patients with grave or instantly lethal COVID-19 infections. This form of therapy perceives a segment of the blood from improved COVID-19 patients imbued into sick patients' bodies. A description by Chinese scientists issued in the journal, 'The Lancet Infectious Diseases' in February proposed the treatment option could be viable in battling SARS-CoV-2. In the US, New York Gov. Andrew Cuomo has proclaimed that the New York doctors will commence recuperating plasma therapy in a trial in late March [49].
- Recently on May 22, Thailand has announced that its Biotech companies developed the mRNA vaccine and going to test it on monkeys after getting a positive response on mice and in the plan for clinical trials on human volunteers.
- By the latest update, *British American Tobacco Production Company* notified that they are going to develop a vaccine based on proteins from tobacco leaves and Patanjali from India also claims to develop a cure against COVID-19, whose major preclinical tests will soon start in Indore and Jaipur [49]. With the gathered information till now, (Figure 2) the contribution of different countries in discovering the treatment against COVID-19.
- Latest update from *Patanjali* in collaboration with National Institute of Medical Sciences, Jaipur discovered an Ayurvedic formulation "Coronil" for treatment and preventive measures against COVID-19, however Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) responded and instructed Patanjali to stop advertising their product till its claims were verified by the

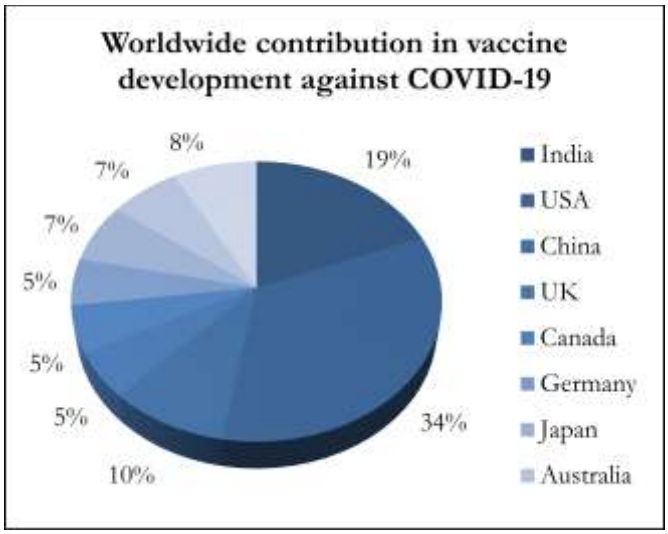

Fig 2. Docking analysis of COVID-19 (a) Validation Showing superimposition, (b) 2-D Ligand H bond interaction in the PDB, (c) Dock pose of most active compound

ministry, and the product given approval [50].

* All data are updated till 24th June 2020.

CONCLUSION

COVID 19 is a novel virus target with properties still being discovered and requiring innovative vaccine technologies. It is a challenge for pharmaceutical industries to develop a treatment for such fatal disease, and still, such sector is working hard, taking it as an opportunity, which opens all the research doors for inventing an antidote/vaccine, which helps to stop the spread of the virus, mitigate symptoms for those infected, and reduces the mortality rate due to the SARS-CoV-2 infection. To assess the potential for vaccine efficacy, several computer simulations, clinical testing specific animal models are being developed. The WHO alliance is reassuring intercontinental collaboration amid officialdoms during the progress of vaccine entrants, nationwide monitoring and strategy agencies, monetary funders, civic healthiness associations, and régimes to come frontward, work in alliances for ensuing engineering of an efficacious inoculation in adequate numbers to hoard all over the world specifically in low-reserve nations. Lessons cultured whilst combating COVID-19 can enable us to curb the upcoming outbreak before it reaches stage III in India. For now, those of us on the sideline can only do our best to flatten the curve.

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NA

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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