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REVIEW PAPER

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A systematic review and meta-analysis on SARS-COVID-2, its molecular virology, transmission & seroprevalence worldwide

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ABSTRACT

In Wuhan, China (2019), an immediate flare-up of corona virus occurred in the human body to introduce a mortal corona virus which not only affects the human health system, but also affect the global economic approach of the world. The virus is the single-chain of positive sensation of RNA that has structural and non-structural proteins. The ACE2 receptor is bound by SARS-CoV-2 in human cells and has its polymerase RNA. While we have seen a big leap in our understanding of corona viruses after two precedents, there are still a few successful methods of treatment and epidemiological surveillance are both important. The corona virus is spreading on a fearful revealing the world that covered the 200 countries in the universe. Current epidemiological and clinical evidences from early Wuhan studies was updated to highlight a range of SARS-CoV-2 features, which differentiate greater fluctuation between the SARS-CoV and the MERS virus of the Middle East (MERS) have been named by the World Health Organization (WHO). The latest clinical trial of the Covid-19 pandemic is systematized. Although studies are currently being performed on different vaccines for the genome of SARS-CoV-2 and therapeutic antibodies, this is a more long-term approach, because it requires a comprehensive safety check.

Keywords: Nucleoside analogs, Remdesivir, Chloroquine, immune-modulating activity.

1. INTRODUCTION

Coronaviruses are enclosed viruses having a single-stranded positive-sense RNA genome and a helical symmetry nucleocapsid. Viruses of the Coronaviridae family are unsegmented. Their huge RNA genome (27–32 kb in size) and club-like spikes (S) that extend from their outer surface to help attachment to host receptors distinguish them [1]. These viruses can infect a variety of hosts and cause disorders in the lungs, intestines, liver, and other organs. The Nidovirales structure and the Coronaviridae family include the Coronavirus and Torovirus

genera [2]. The particular mechanism of replication, CoVs continue to be recombined and mutated and can thus continually acclimatize to new hosts and ecological niches [3]. Despite wide variation in genetic and viral architectures the viral replication mechanism involves the development of multiple nesting substrates RNAs (mRNAs) for 3' like termination are characterized by a family of viruses named the Coronaviridae, Arteviridae, and Roniviridae. The subfamily of Coronaviridae is distinct in viral morphology and genome size from the Torovirinae [3]. Corona viruses are present all over the world where human coronavirus only infects humans and causes severe respiratory infection, and also present in several species of animals [4]. There are several classes of coronavirus in human SARS, MERS, human coronavirus and Bocavirus are some of the viruses that have been identified by the World Health Organization in recent years [5]. In 2003, a coronavirus outbreak caused severe acute respiratory syndrome (SARS) causing 8096 reported cases around the globe with 774 deaths. Exotic mammals such as palm civets and raccoon dogs in wet markets are known to be animal vectors of the virus for the 2003 SARS outbreak [6]. The coronavirus SARS has discovered in these species resulted in a temporary sales ban in 2004 preventing further spill over from animals to humans [7]. Nonetheless, additional monitoring study indicates that these animals in non-market conditions are rarely positive for SARS coronavirus and suggests that they were only intermediate hosts during the case [8]. MERS CoV is the reason for critical inhalation septicity. Research workers explained that the virus was transferred from camel to human, MERS virus was started in camels from Africa, Middle East, and Asia [8]. In 2012, CoV of the Middle East Respiratory Syndrome (MERS) reason for critical inhalation and excretory organ disease nearly 90 patients were reported worldwide [9]. For SARS-CoV and MERS-CoV respectively the death rate was 10% and 37% [5]. The CoV that has previously been identified could only represent the tip of the iceberg, as there are likely to be numerous more unusual and serious zoonotic occurrences to be discovered [9].

Many incidences of an unknown COVID-19 origin occurred in the Chinese city of Wuhan, in the province of Hubei during December 2019 and the clinical presentations were very close to viral pneumonia. A cluster of patients with unexplained pneumonia was related to the Wuhan Seafood Wholesale market in Chinese Wuhan in December 2019. The use of objective sequence within samples of patients suffering from pneumonia has identified a previously unknown beta coronavirus. A new 2019 coronavirus from a clade was isolated from human epithelial cell airways in the subfamily Orthocoronavirinae [10].

Following the advent of this novel viral illness, the International Committee for Victim Taxonomy allocated Cob classes (Core ontology for biology and bio-medicine) to distinct genes, namely Alpha, Beta, Gamma, and Delta CoV. Several other CoVs were subsequently found in animals and also present in humans. As a result of the tradition of walking in flocks and long journeys, the majority of new viral strains were deposited with birds and animals [11]. Birds are also able, between themselves and humans, to

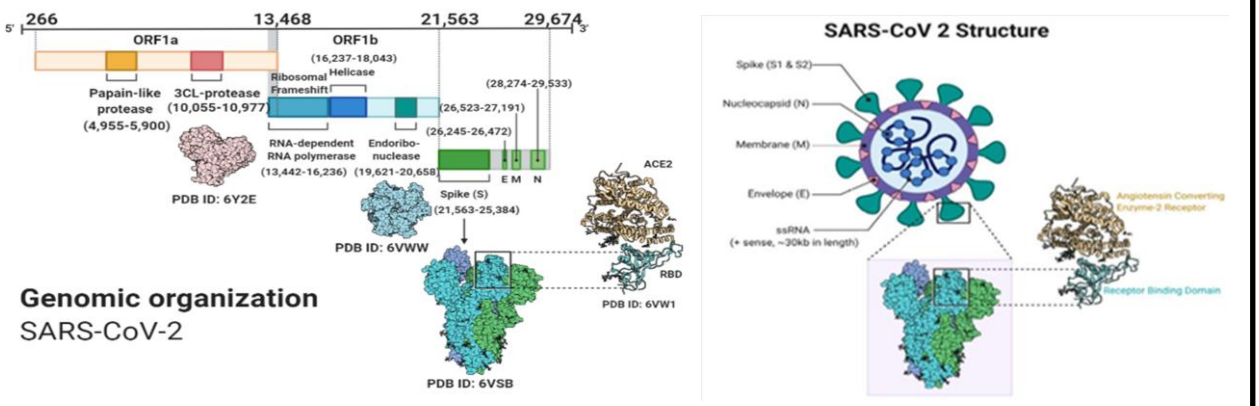
transmit the emerging viruses. The migration of birds and bird species diversity in China can contribute to a wide variety of pathogens, including the introduction of CoV. A public health position should also be considered as the original studies of these viruses, SARS-CoV-2, severe respiratory syndrome (SARS-CoV), in the middle east, for example, can aid agents who can cause respiratory failure [12].

1.1. Epidemiology

The first four cases of an idiopathic acute respiratory illness were reported in Wuhan City, Hubei Province, China, on December 29, 2019. It was a research that the people were most at threat having communities with weak immune systems that are older people and those who have kidney and liver disorders. The COVID-19 has been examined that it has greater levels of infection and epidemic threat than SARS-CoV. The actual procreation figure (R) of CoV-19 is investigated to exist greater than arrived actual procreation figure (R) of SARS. The most recent research and suggestion from the Chinese health jurisdiction stated a total training 7-day period, ranging from 2 to 14 days [13]. Human CoV was tested by ELISA in nasopharyngitis. The Mucus was drawn and 30 % of 108 nasopharynx septicity was tested by 30 children under age 6 years with repeat inhalation septicity and 29 % out of 51 serious respiratory septicity was investigated by their family. Lower respiratory tract contamination is dominant in wheezy bronchitis-occurred in 30 % of the clue infant, corona virus-positive infections but in none of their family contamination. Two peaks of contamination were observed every year in the last autumn/early winter and in the early summer [14]. On January 20, 2020, the first kid case was reported in a 10-year-old boy from Shenzhen, China, whose family had served in Wuhan City. However, hospitalized for inhalation septicity COVID-19 was detected in 6 infants (1.6%) between January 7 and 15, 2020, with the onset of infection occurring between January 2 and 8, 2020. This survey consequence shows that SARS-CoV-2 contamination in pediatrics was diagnosed in the early pandemic [15].

1.2. Sources of coronavirus

Researchers investigated the source of the



A B

Figure 1 A: Genomic organization of SARS-CoV-2 [86]; 1 B: SARS - CoV 2 Structure [87]

critical acute inhalation disorder that has change into their awareness of the wild-animal trade of southern China [16]. The term "coronavirus" comes from the Latin word corona, which means "crown". The coronavirus can cause a variety of diseases in mammals and birds, including enteritis in cows and pigs, upper respiratory disease in chickens, and potentially fatal human respiratory infections [1]. CoVs can cause disease in a wide range of domestic and wild animals, as well as humans, with and-CoVs infecting mammals and and-CoVs infecting birds. SARS-CoV and MERS-CoV, two extremely virulent -CoVs, have triggered pandemics in humans since 2002. SARS-CoV was first discovered in China and subsequently spread to other regions of the world, infecting roughly 8000 people in total. During the pandemic of 2002–2003, 10 % of people died. MERS-CoV has spread to 27 countries since its discovery in the Middle East in 2012, resulting in 2249 laboratory-confirmed cases of infection with a 35.5 % fatality rate (until September, 2018). Beside these two viruses, - CoVs 229E and NL63, as well as -CoVs OC43 and HKU1, can cause respiratory infections in humans [17]. Coronaviruses (CoVs) cause a wide range of diseases in domestic and wild animals, barnyard fowls, and rabbits, including mild to severe intestinal, respiratory, and systemic disease, as well as the common cold and pneumonia in humans. The occurrence of patients with pneumonia of unidentified cause was reported to WHO by Chinese national authorities on December 31, 2019. The coronavirus study group named this virus severe acute respiratory syndrome corona virus-2 (SARS-CoV-2), and the current corona virus-associated acute respiratory illness outbreak was named coronavirus disease 19 (COVID-19). The first instances of COVID-19 were discovered in Turkey on March 10, 2020, with a total of 47,029 cases and 1006 deaths after one month. SARS-CoV-2 infections are increasingly widespread, with 1,727,602 cases documented in more than 210 countries as of April 10, 2020, and 105,728 deaths [18].

1.3. Structure and genome organization of SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus with a genomic size of 30 kb that belongs to the Coronavirus subgroup and the Coronaviridae family. SARS-CoV-2 has a genome that is similar to that of other coronaviruses, with 10 open reading frames (ORF3a/b, ORFs, ORF3a, OF3b, ORF6, ORF7a, ORF7b, ORF8a/b, ORF9b, ORF1a) [19]. The first ORFs (ORF1a/b), which make up at least two-thirds of viral RNA, change into the pp1a & pp1ab polypeptides, which are then cleared into non-structural proteins [20]. The whole-genome adjustment of SARS-CoV-2 is different from patients which were living or fall upon in Wuhan that indicates a genome 29 844 to 29 891 in size. The coding which all over 9860 and lacks the haemagglutinin-esterase gene [21].

The CoV nucleo-capsid (N) is a structural protein conformation multiplex with genomic RNA, during virion convocation, it is related to the viral membrane protein and plays a vital role in enhancing virus transcription and convocation organization [22]. The encapsulated virions have a diameter of around 100 nm and are connected by broad, petal-shaped spikes.

The spikes are oligomers of 180–200 kDa, S glycoprotein attaches to glycoprotein receptors and induces viral envelope fusion with cell membranes and, in some cases, cell division. A set of coronavirus S proteins is also associated with 9-O-acetylated silica acid. M glycoprotein is a tiny glycoprotein envelope that crosses the lipid bi-layer three times and attaches to the nucleo-capsid in the virion. Intracellular transfer to the M glycoprotein is detained at the Golgi, which may regulate coronavirus intracellular unfolding. The tiny E glycoprotein, which appears to be a nu-structured protein at first glance, is found in modest amounts in virions and is required for virus unfolding. Some coronaviruses include a hemagglutinin-esterase glycoprotein (HE) in their envelopes, which looks like little spikes and binds N-acetyl-9-O-acetylneuraminic acid or N-glycolylneuraminic acid while also having esterase activity. The monopartite, linear, single-stranded genomic RNA is encapsulated by the nucleocapsid protein N. Coronaviruses were once thought to have a helical nucleocapsid as their internal structure.

2. REVIEW OF LITERATURE

Yang *et al*., (2020) conducted a study in 2020 on a current global wide pandemic of the novel corona viruses [23]. The pandemic was starting from Wuhan in China & reached the other 66 countries. Government is sticky to finish the breakout of the pandemic. In this phase, the translucence and steps to control are activated. The Sars-CoV-2 infected cases have symptoms of fatigue, dry cough, dyspnea, etc and physical examination CT SCAN, tests are used in the diagnosis of this pandemic. Hence only bed rest and some supportive anti-viral medications are used to treat these diseases [24].

Yuthana Joyjinda, *et al*. (2021) has stated that discovery of RaTG13 bat corona virus in China suggests that bat origination is at its peak [25]. In Southeast Asia, he described genetic and serological evidence of SARS-CoV in bats. SARS-CoV-2 neutralizing antibodies were also discovered in bats, therefore he collected complete genome sequences from 5 different bats. SARS-CoV-2 was cross-neutralized by anti-sera generated against RmYN02's receptor-binding domain (RBD). Despite the fact because RmYN02's RBD failed to bind ACE2, cross-border ("transnational") examination is required to locate the SARS-CoV-2 immediate progenitor virus [26].

Kurt Wibmer, *et al.* (2021) it observed that SARS-CoV-2-501Y.V2 is a new corona virus lineage that causes Covid-19 and has mutations in two immune dominant regions of the spike protein [27]. Confirm that a pseudo-virus producing the 501Y.V2 spike protein is immune to three types of therapeutically important antibodies. This pseudo-virus is also immune to neutralization, but it does not bind to convalescent plasma [27].

Hu.*et al*., (2019) has been reviewed that serve-acute respiratory syndrome coronavirus-19 [7]. He also described the genomic characteristics of SARS-Covid-2. He evaluated that SARS-CoV-2 infection is spread to people of all ages. However genomic monitoring of SARS-Covid-2 is needed worldwide to promptly identify mutation that causes the phenotypic changes of viruses. Hence Covid-19 is challenging all human beings. It has

been conducted that corona viruses are a diverse group of viruses that can infect both animals and humans. In this study he analyzed that at-least seven families of corona viruses are caused respiratory infection in humans. 4th classes of these families cause common cold like infection. SARS-CoV-2 viruses cause Covid-19, a respiratory ailment that was declared a pandemic in March 2020.

Kavita Narang, *et al.,* (2020) it has been observed that SARS-CoV-2 epidemic on a global scale [28]. It has been linked to poor outcomes in a variety of patient groups, including the elderly and those with co morbidities. Pregnant women may be at a higher risk of infection-related morbidity and mortality due to seasonal influenza. SARS-CoV-2 infects cells through the (ACE2) receptor, which up-regulation of ACE2 mediates conversion of argiutensin11 to argiutensin (1-7) vasodilation cause low blood pressure and up-regulation of renin-angiotensin-aldosterone system cause increase ACE2 expression in pregnant women cause SARS-CoV-2 infection [28].

It has been stated that the T cell immunity case of Covid-19 and SARS control. In this study, He described that Memory T cells activated by earlier virus can form vulnerability to seventy and subsequent infection. T-cell respond the structural & non-structural part of SARS Covid-2 in specific recuperate from corona viruses diseases. Patients who recovered from SARS linked to SARS Covid had a long larling memory and T-cells that are reactive to SARS Covid's N-protein [29].

3. REPLICATION CYCLE

The corona virus viral particle consists of structural proteins, such as spike (S), envelope (E), membrane (M), nucleo-capsid (N), and, in a few beta corona viruses, haemagglutinin-esterase; make up the corona virus viral particle. During the convention process, the positive-sense, single-stranded RNA genome (+ssRNA) is encased N, while M and E protected its embodiment in the viral particle. S-trimers evolved from the viral envelope derived from the host and give cellular entrance receptor selectivity. Corona virus molecules bind to cellular factors, and the particular S protein interacts with cellular receptors (such as (ACE2)) and host factors (TMPRSS2) that burst the un-coating of the coming-in genomic RNA and subject it to the real translation of two big open reading frames, ORF1a and ORF1b, that induce viral uptake and fusion at the cellular or endosomal membrane. They are made up of poly-proteins pp1a and pp1ab, which are co-transitionally and post-transitionally processed into the non-structural proteins (nsps) that make up viral replication and transcription complex. In line with understanding of nsps, the biosynthesis of viral replication organelles, which include essential perinuclear (DMVs), (CMs), & (DMSs), produced a protective micro-environment for viral genomic RNA replication and transcription of subgenomic mRNAs (sg mRNAs), which include the specific set Translated structural proteins enter the endoplasmic reticulum (ER) membranes and pass via the ER-to-Golgi intermediate compartment (ERGIC), where they interact with encapsulated RNA to create genomic RNA, which results in secretory vesicular compartments budding into the lumen. Finally, exocytosis

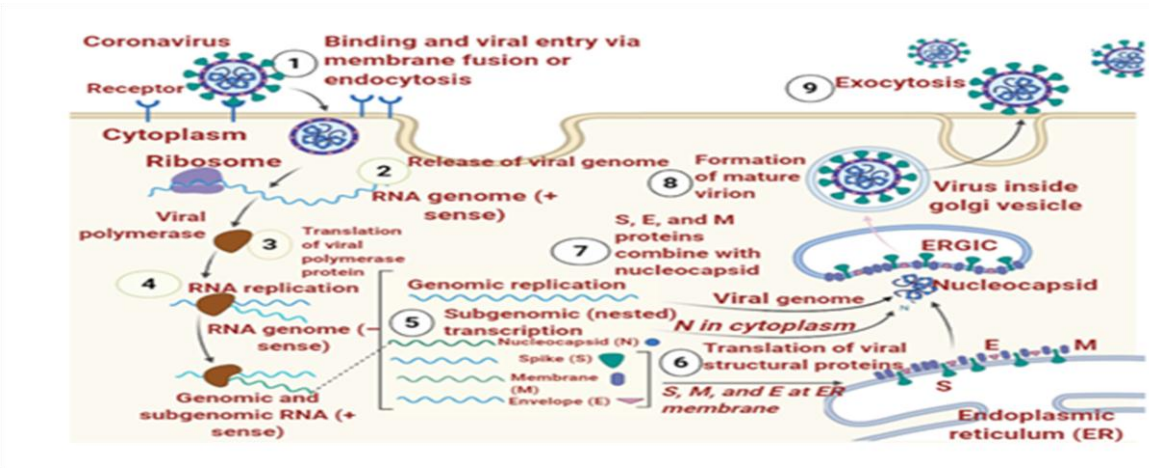


Figure 2: Replication Cycle of SARS-COV-2 [87]

removes virions from the septicity cell. The stages that are blocked by chemicals and are directly conformed to create the appealing antiviral targets are highlighted in red. dsRNA, double-stranded RNA; L, leader sequence; An, 3′ poly A sequence; cap, 5′ cap structure; RNA-dependent RNA polymerase (RdRP) is a type of RNA polymer [25].

4. CLINICAL AND RADIO-LOGICAL FEATURE

The entire clinical course is not yet indistinct, as the warning sign recorded are minor to extreme, some even death. The specific symptoms reported involving headache, vomiting, hemoptysis, runny nose and cough. The most frequently found are nausea, coughing, or weakness, bronchitis and severe dyspnea. Many death cases were Pre-existing problems in middle-aged and older people (cancer cell operations, cirrhosis, high Bp, coronary heart disease, diabetic, and Parkinson's disease) [13]. The following symptoms are defined in Case Description Guidelines: fever, reduction in white blood cells and lymphocytes, new chest x-rays, and no improved symptoms after three days of antibiotic treatment [30].

Although COVID-19 diagnostics can be suspected of being pneumonia in a patient's recent trip to China or connection to the patient\chest imagery perform a significant part in the evaluation of some the severity of disease and the follow-up. Chest x-rays typically show asymmetric airspace opacity patchy or diffused, closer to the other corona virus pneumonia cases [31]. The first study of COVID-19 patients identified bilateral lung contribution in preliminary chest CT among 40 of 41 patients, consolidating trends seen in ICU patients and mostly ground glass patterns in non-ICU patients [32]. Initial COVID-19-positive CT results in 21 people validated, have been examined and irregular findings identified in 86 % of patients with bilateral lung involvement [33]. Similarly the chest imaging showed bilateral patched floor glass opacity and greater lung participation among older family members of the Multi-focal floor glass opacity and consolidation at 57 % and 29 % in the recorded COVID-19 family of seven men, respectively, with the peripheral pneumonia preferences

[34]. Although the features of the pictorial images closely look into those of MERS and SARS, both lungs contain COVID-19 more often. Initial chest picture anomalies in SARS and MERS more often are unilateral. For patients with COVID-19, researchers are not aware of pleural effusion, cavitation, pulmonary nodules and lymphadenopathy. One out of 99 COVID-19 confirmation patients had pneumothorax identified, but the unknown was whether pneumothorax was a straight corona-virus obstacle [31]. The importance of early CT results for the finding of the disease was shown in a study of five long-established CoV-19 patients, who obtained a positive swab virus test result at first. This study showed that it could help to initially investigate individuals suspected to be a virus by the existence of standard CT tests [35]. Initial imaging, however, has been confirmed to show normal findings in 15% of the patients, which does not preclude an infection by a regular chest imagery test. Since chest representational process is an essential part of patient care for people with COVID-19, more work is compulsory to progress the understanding of image findings across the entire course of the disease [36].

5. DIAGNOSTIC TESTS

5.1. RT PCR

RT-PCR kits have been formed to genetically find SARS-CoV-2. RT-PCR involves the additional DNA reverse transcription (cDNA) strands of SARS-CoV-2 ribonucleic acid and accompanied by amplification to different cDNA regions [37-38]. The test can be configured as a two-target system, with one first uniformly detecting a larger amount of corona viruses, like SARS-CoV-2. RT-PCR is most common method used to use respiratory samples to examine COVID-19 [39]. Using a 1-stage, real-time RT-PCR (rRT-PCR) trial that offers quantifiable data about viral loads, the United States Cents for infection measure and Preventative (CDC) detects the presence of SARS-CoV-2 [40]. The study is carried out by removing the viral RNA and applying it to a master mix (Fig 3). The master mix includes water free from nuclease power, forward and reverse primers (Transcriptase, Polymerase, Magnesium, anti-free radioactive nucleotides and additives, a fluorophore sample and a reaction mixture). In a PCR thermocycler, the master mix and the collected RNA are positioned and the incubation temperature is set to begin the experiment. The fluorophore quencher is split and a fluorescent signal is produced during the RT-PCR [41]. The RT-PCR. Cycling conditions are recommended by the CDC. The thermocycler senses the fluorescent signal and tracks the amplification progress in real-time. The RT-PCR takes 45 minutes and can be performed on a 96-wave plate with a different sample or control for

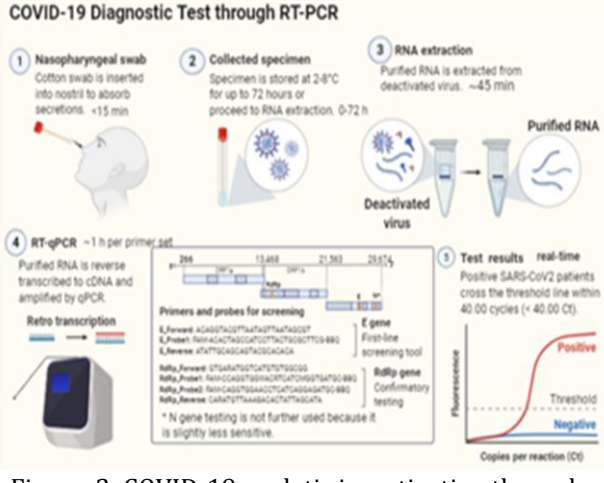


Figure 3: COVID-19 analytic investigation through RT-PCR [86]

each well. The final results of the RT-PCR must be interpreted correctly both in a positive and a negative way. The CDC has provided a positive control sequence for SARS-Cov-2 called nCoVPC [42].

5.2. IgM ELISA

ELISA was highly suggested and predictable to advance CoV-19 detection, because detection of viruses by blood sampling was far less serious than the detection of nasal or oral swab, and antibodies permit much more time than viruses for detection [43]. In addition, ELISA was able to reverse rapidly and cost relatively low. ELISA procedures should make up the RT-PCR deficiencies [24]. SARS-CoV Rp3 nucleo-capsid protein ELISA system for detecting immunoglobulin M opposing SARS-CoV-2 in start COVID-19 cases have been successfully developed [44]. The warning is, ELISA can produce results that are incorrectly positive because N protein is the most basic human viral protein of β-corona virus [45]. Antigens used in ELISA will respond to four other CoV antigens in common colds with antibodies. S protein is the utmost complex protein that can be a successful ELISA production candidate [45].

Spike proteins are large and have two domains near amino and carboxyl terminal. These spike proteins play role in the attachment to receptor and membrane fusion during virus entry. Research showed that changing in virus virulence is related with difference in spike gene. The one domain S1 can bind to cellular receptor and integral membrane S2 domain can enhance the synthesis of biological and viral membranes [2]. Spike protein of SARS-Cov-2 has vigorous binding attraction with individual ACE2 receptor [46]. SARS-Cov-2 identifies ACE2 receptor much significantly than SARS-CoV which showed its person to person spread [47]. Therapeutic strategies include SARS-CoV-2 vaccine for spike protein, TMPRSS2 inhibition of spike proteins for priming, blocking ACE 2 or peptide usage of surface receptor, and soluble ACE2, which prevents viral cell entry by binding SARS-CoV-2 competitively and decreases viral loads [2].

5.3. Protease and papain like protease inhibitor

Beta corona virus upon transcription produces poly-peptide which is cleaved by proteases into several proteins. Pro-teases use are papain-like protease and 3-chymotrypsin same protease. The 3CLPro create poly-peptide at 11 sites to produce non-structural viral proteins that have role in virus replication and its located at 3' end of genome, It's a major target for coronavirus inhibition [48]. Non-structural proteins of SARS-COV-2 genome play role in RNA transcription, translation, protein synthesizing and modifications. Among these proteins 3CLPro and PLpro are targeted to inhibit by small molecular inhibitors. N-terminus of replicase poly-protein is cleaved by PLpro which important for virus replication. The screening showed that antiviral drug has strong binding affinity with PLpro. 3CLPro promotes the maturation of non-structural proteins that is crucial for virus life cycle. Several natural compounds and derivatives with anti-viral effects have full constricting affinity to 3CLPro [24]. Anti-corona viral activity is in vitro to lopinavir and/or ritonavir. Most studies in vitro have exposed that lopinavir can inhibit SARS-

CoV and lopinavir's EC50 is appropriate. In the Vero E6 compartment with the approximate EC50 of 26.63 μM Lopinavir displayed an antiviral action across the SARS-CoV-2 virus [49]. SARS studies shown that LPV / r take part an important function, especially at early stage, in clinical outcome. The danger of severe respiratory distress syndromes (ARDS), and expiry due to SARS-CoV was lower, 2.4% vs. 38.8%, on day 21 following the beginning of warning sign, relative to ribavirin alone in a Hong Kong study [50]. In New Year Ivermectin proven to be an antiviral agent with a wide variety of in vitro viruses approved by the FDA. The interaction between the integrase-1 (HIV-1) integrates protein human immunodeficiency virus and the importing (IMP) 1 hetero-dimer accountable for the integrase protein import, was initially known as an inhibitor [51]. Other functions of ivermectin described, only ivermectin has performed great role to control the central import of parasite and viral proteins. Ivermectin was discovered in an in-vitro learning to be a SARS-CoV-2 inhibitor, with a single addition of 2-hour post-SARS-CoV-2 cells to Vero-hSLAM that can minimize virus RNA at ~5,000 times as much as 48 hours. Researchers conclude that it is possible that viral protein (as shown by other RNA viruses) is inhibited by an the virus's innate immunity mechanism is disrupted by IMP/1-mediated central import and regulation [53].

5.4. RNA Polymerase inhibitor

Remdsivir: SARS-CoV-2 infection is also treated with antiviral interferons, antibiotics, neuraminidase, RNA synthesis inhibitors and Chinese conventional medicines. So, to find drugs against the disease it is better to test the already available drugs to check either these drugs show antiviral property against the SARS-CoV-2 or not [43]. Remdsivir has shown promise against a variety of RNA viruses (including SARS/MERS-CoV5) in cultivated cell, mouse, and non-human primate (NHP) models. Remdesivir is now being tested in clinical trials to treat Ebola virus infections [54]. Remdesivir is equivalent to adenosine that incorporates into nascent viral RNA chains, leading to immature ending. Remdesivir shows functions at the place virus entry point. As Warren, Jordan *et al*. (2016) also reported its 100% protection against the infection Ebola virus after the intravenous administration in the NHP model [55]. Remdesivir also showed inhibition of virus infection effectively in a human cell line that is open to SARS-CoV-2 [56].

5.5. Favipiravir

Favipiravir (RNA polymerase inhibiting antiviral agent (RdRp)) are selectively and potently. Favipiravir undergo intracellular phosphoribosylation, which is recognized by RdRp as the substratum, to be involved and inhibits the activity of RNA polymerase and favipiravir ribofuranosyl-5B-triphosphate (Favipiravir) [57-58]. A single-stranded beta-CoV RNA sequence with RdRp gene identical to SARS-CoV and MERS-CoV was found in the 2019-nCoV Genome. Favipiravir is therefore regarded as a prospective candidate for CoV-19, although in vitro and pre-clinical animal-like work has yet to be confirmed. Favipiravir in Vero E6 cells with an EC50 of 61,88 μMol is inhibited in an in vitro trial of SARS-CoV-2 [59]. Nevertheless, in other favipiravir research, there

was no clear in vitro antiviral outcome on the SARS-CoV-2 at concentrations below 100 μML [49].

5.6. Chloroquine

A wide antiviral medication with a long history of usage as an auto-immune and anti-malarial drug is known as Chloroquine [60-61]. Chloroquine act as antiviral drug and this drug increase the endosomal pH that is necessary for cell fusion and blockage viral infection. In addition to blocking the virus infection, this drug also interferes with the cellular receptors of SARS-CoV in the process of glycosylation [62]. Like Remdesivir, Chloroquine also functioned at the entry stage in addition to post-entry stages ofSARS-CoV-2 septicity. In addition to antiviral act, this drug also helps in the regulation of immune system activity that may boost its result in-vivo. Later oral examination of Chloroquine rapidly distributes in the whole body. For the last 70 years, Chloroquine has been used as a drug due to its safe and cheap property. That's why it can potentially use againstSARS-CoV-2. According to the reported data Chloroquine and Remdesivir showed a more effective result in vitro against SARS-CoV-2 infection [43].

5.7. Hydroxychloroquine

Chloroquine has a similar mode of action, however the same mechanism of action as Chloroquine, but is made the favored medication to treat malaria and autoimmune disorders by its tolerable safety profile. It was observed, in vitro, that hydroxychloroquine (EC_{50} = 0.72 μM) is many active than Chloroquine. Supported on the findings of the PBPK models, for SARS-CoV-2, the charge dose 400 mg of hydroxyl-chloroquine sulfate is suggested twice daily, and for SARS-CoV-2 infections the presence of 500 mg twice daily is continued with 200 mg for 4 days [63].

It is is an inhibitor of influenza viruses and arboviruses approved by Russia and China. Arbidol, the main glycoprotein on the flu virus surface, prevents the virus membrane fusion with the endosome following endocytosis by targeting hemagglutinin (HA). Research in the form of a single agent (NCT04260594, NCT04255017), is currently underway. The latter was shown to be much better Arbidol and favipiravir were compared in treatment outcomes in a randomised controlled trial [64].

6. IMMUNE RESPONSE

The twenty-first century is facing a continuous threat from third zoonotic human beta coronavirus as there are no appropriate drugs for its treatment. This is because the exact mechanism of infection is still not known. T cells are activated and differentiated as a result of coronavirus infections. This ultimately results in the massive production of cytokines for amplified immune response. Scientists have found that S- protein is responsible for coronavirus infection as the C terminal RBD domain of the S1 unit makes it easier for the pathogen to attach to the donor receptor ACE2 [65]. Several sequences of RBD domain at positions 442, 472, 479, 487 and 491 responsible for cross specie transmission in SARS CoV-Tor2 and HP03-GZ01 have high homology with Wuhan CoV (SARS-CoV-2) [47]. Out of these five only Tyr491 is preserved in Wuhan CoV (SARS-CoV-2) [65]. Upon infections

certain cytokines and chemokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) are released to combat the infection by the production of leukocytes and lymphocytes [66-67]. The most effective is produced by CD8 T cells [68]. Entrance of dsRNA of corona is recognized by TLR-3 and TLR-4 which activate the production of pro-inflammatory cytokines via MyD88-dependent signalling pathway and type I IFNs. These are the essential signalling proteins for the regulation of immune system through a cascaded of signalling pathways (regulation of IRFs and NF-KB) [69]. Signalling of TLR-3 can be blocked by some accessory proteins of coronavirus which facilitates pathogen entry and replication in the host [47]. During replication, these proteins bind with the dsRNA of CoV to inhibit TLR-3 activating and help the virus evade the immune result. Nucleotide-binding & oligomerization like receptor (NLRs) identify pathogens and divided into 3 sub-classes on the basis of function they performed. First class NLRs bind with proteins called inflammasome having eight NLRs proteins. The second class of NLRs performs role in reproduction while the third class is regulatory NLRs, using these receptor systems host immune response detects viral infection [70]. SARS-CoV special T cells are screened in SARS-CoV patients indicated that T cells reaction are focused on SARS-CoV structural proteins. SARS-CoV membrane and nucleo-capsid response with two CD8+ T cells are detected. T cells respond to viral spikes, membrane and nucleo-capsid are long-lasting showed by research [70].

7. CLINICAL TRIALS IN DRUG

There is currently inadequate information for successful management of COVID-19 pneumonia by any existing anti-viral medicines. However, few clinical trials have been performed on possible antiviral therapies. Depending on their purpose, the therapies can be classified into two groups. One is acting directly on the coronavirus by impeding the critical genome replication viral enzyme or by blocking the entering viruses into individual cells. The different is intended to control the human immune arrangement, either through an improved internal reaction to viruses or by inhibitions of inflammatory processes. Thalidomide in recent re-emerged as an anti-angiogenic, antimicrobial and anti-fibrotic mediator. It was used to treat numerous inflaming illnesses such as Crohn's and Behcets' diseases by decreasing the synthesis of TNF-α. Preclinical research have shown thalidomide to use infected mouse with H1N1 via a reduced in inflammatory cell infiltration and pro-inflammatory cytokine growth. The immune-modulatory reaction of thalidomide, which may reduce the cause of lung damage is excessive defense to SARS-CoV-2 have been investigate in the restart studies (NCT04273529, NCT04273581) [71]. BevacizumabIn patients with severe inhalation discomfort disease, and raised endothelial growth factor (VEGF) was noticed. VEGF serve an endothelial harm mediator and enlarge micro-vascular permeability. The humanized, monoclonal antibody Bevacizumab regularly used in numerous cancers, can avoid angiogenesis with VEGF binding. The efficiency of Bevacizumab as a specific solution to SARS-CoV-2 is being tested in an on-going study (NCT04275414) [72]. Fingolimod is an anticancer used especially for

the treatment of several refractory sclerosis. It may be a great role antagonist of the S1P1 receptor in lymph node T cells look like lipid sphingosine 1 phosphate (S1P) structurally. The strong binding mechanism of internalizes the S1P1 receptors and segregate the T-cells of the lymphatic node. Decreased T lymphocyte pulmonary influx is another solution to uncontrollable immune - pathogenesis (NCT04280588) [72]. The virus cells produced antibody type I. These have a broad, anti-viral activity against HCV, inhalation syncytial virus, SARS-CoV used only in conjunction with other treatment. In this treatment of COVID-19 pneumonia (NCT04293987), examined present on their protection and strength [75]. Mesenchymal stem cells (MSC), reducing the amount of unhealthy cytokines and start paracrine factor to regenerate the tissues, have tested to be anti-inflammatory drug. Pre-symptomatic proof has determined that MSCs not only can better endothelial permeability, but also lower inflammatory penetrate. Their function in the pneumonia of COVID19 is still being studied, although the anticancer effects(s) of MSCs have explained naval influenza viruses. Presently, (NCT04293692, NC T04269525, NC T04288102, NCT0430250) are being protected for NSCs from the umbilical cord or dental pulp [43]. As earlier stated, the organized glucocorticoids in SARS-CoV-2 disease are presently contraindicated, as viral consent will continue. It's also confirmed, however, that COVID-19 pneumonia vital pathogens contain both of the direct harm from the virus and the host's extra immune response. Therefore, the discussion over even if the administering of methylprednisolone can support to finish undesired immune reactions is still contentious (NCT04273321, NCT04263402) [75]. SNG001the capacity to inhale the medicine would require a small, handheld atomizer to auto administer the medicine. Produced for chronic obstructive (COPD) extreme lung disease, it was rapidly immediately in a new 100-patient clinical testing due to the continuing COVID-19 crisis [76]. TocilizumabIt is an antiviral drug, which segment IL-6 productive in seriously ill COVID-19 patients during cytokines storms. Chinese herbal medicine used in 2003, the consequence were decreased hospitalization, reduced steroid-related opposite reactions, and convert in the infection of persistent with the severe acute respiratory problem (SARs) provide with herbal medicine (Organization). Mostly the new coronavirus' genomic and structural silicone nature showed that they are nearly associated with SARS and express herbal medicine may be possibly employed in the current outbreak. The in-silico methods of control herbal medicine treatment that could directly stop coronavirus reproduction is start in the Journal of medical care issue [10]. There were two present screening principles: oral efficiency to avoid viral infections moreover selectivity of patient phenomenon. Anti-novel coronavirus chemical substance that attains oral necessary should be combined in the herbal medicine treatment. Selected and tested for potential related with respiratory SARS coronavirus or Middle East syndrome were a representation of natural compounds. Then, the propriety of these chemicals for oral administration was checked. The structural compositions of these natural chemicals, in particular, their capability to act or

dock with the principal proteins of new coronavirus were evaluated. Their strength prevent new coronavirus disease was showed by positive docking. The researchers control a more three rounds of screening in order to follow the patient's manifestations. Such methods convey to decrease the large compound libraries into a subset with particular resources in an approximately short period of time and give guidance in the further clinical application of herbal medicine formulas. The efficiency and protection in some compartment culture furthermore animal testing of the detection of the chosen 26 herbaceous plant are examined. Finally, herbal medicine therapies should be proved for the prevention, diagnosis as well as recovery of patients with novel coronavirus respiratory disorder in safely arrange clinical trials, whether only or incorporated in western medicine [77].

8. CLINICAL TRIALS ON VACCINE

Vaccine production is a longer-term strategy for avoiding potential COVID-19 outbreaks. Several nucleic acid-dependent vaccine candidates were suggested for the sequencing of genome SARS-CoV-2, mainly supported on the S protein code sequence. In overdose of 90 antibodies are being composed in proceeding of SARS-CoV-2 view into grouping in system over the world. Research-based are proved many variation, a few of which haven't been proper in a legal antibody permeable. At some estimate six assembly have accurate begin inspire explanation into participant in well-being preparation; others have started testing in animals. Modern mRNA-1273 is a artificial mRNA strand that encodes the viral spike protein that is perfusion-stabilized. It is predicted that antiviral response specifically to SARS-CoV2's spike protein will be elicited after intramuscular injection into human beings. In addition, the synthesis of a lipid Nanoparticle-encapsulated mRNA vaccine needs no virus unlike traditional vaccines, either made from inactivated pathogens or from small sub-units containing live pathogens. It is therefore fairly safe and ready for testing. If mRNA-1273 is safe for humans and the phase I test is completed, a successive effectiveness evaluation is immediately performed [75]. INO-4800Inovio Pharmaceuticals has developed INO-4800 as a candidate for DNA vaccine. Moderna's mRNA-1273, INO-4800 is a hereditary vaccine that can be converted into proteins in human cells to produce immune responses. Genetic vaccines need lower manufacturing costs and simpler methods of treatment than traditional vaccines. A simple nucleic acid structure also avoids the risk that recombinant protein-based vaccines could lead to incorrect folding. The quantity of plasmid given and the correct period and way of management are, however, the element that may affect genetic vaccine immunogeneic [78-79].

An alternate move to integrate antigen is Platforms based on nanoparticles. By encapsulation or covalent functionalization, antiparticles can be combined with antigenic epitopes, imitative viruses, and trigger antigen-specific lymphocyte proliferation and cytokine release. Intranasal or oral vaccines can potentially generate systemic immune responses in addition to activating immune function on the mucosa's surface. It demonstrates the efficacy of Nanoparticle-based

vaccinations to protect humans against respiratory viruses that cause systemic symptoms. Novavax, Inc. is working on a nanotechnology vaccine based on coronavirus S-protein antigens. In the baculovirus system, the protein is stable, and it is projected to enter phase I this summer [80]. ChAdOx1 nCoV-19 Infant and humans with basic diseases, the non-replicative residence of adeno virus in the owner makes it moderately healthy. In insertion, Adenovirus-based direction are remarkable by extensive of tissue tropism envelope the two major section of ACE-2 SARS-CoV-2 receptor, the respiratory and epithelial duct. But it is also essential to consider the measure of dominant resistance to the vector genes and not the trans-genes. Non-replicating SARS-CoV-2 adenovirus vector and S protein genetic chronological sequence were improved by the University of Oxford and have been refer into the Phase I / II pharmaceutical study (NCT04324606) [81]. Pathogen-Specific Artificial Antigen-Presenting Cells informed that antigen-specific T cells can devastation cancer cells and viral infections in a punctual way, producing sizeable numbers of viral antigen-specific T cells may healthy change us to resist the SARS-CoV-2 spreading. Sufficient antigenic T-cells that initiate T-cell effectors, as well as the development and activation of cytotoxic T cells give efficient methods for producing large amount of cells. Report have now been conducted in conjunction with the antigen limited cytotoxic T cells regulate the protection and immunogenicity for a APCs only (NCT04299724, NCT04276896) [82]. Ad5-nCoV the vaccine is related as Ad5-nCoV based on its adenovirus composition. Phase I clinical trials are performed in healthy individuals aged 18-60 in Wuhan, China under the Chinese Clinical Trials Register [76]. Alt immune, IncA one-dose, intranasal, adenovirus vaccine that contains protein SARS-CoV-2S is presently studied. The vaccine is being tested in animals at this time. LV-SMENP-DCIn this vaccine DCs changed with lentiviral vector communicating manufactured mini-gene dependent on areas of chose viral proteins, controlled with antigen-explicit CTLs [83]. Virus vaccines seven groups are creating immunizations change the infection itself, in a debilitated or inactivated structure. Many existing antibodies are made along these lines, for example, those against measles and polio, however they involve broad security testing. Sinovac Biotech in Beijing has begun to test an initiate adaptation of SARS-CoV-2 in people. By using chemicals viruses are inactivated to make this vaccine, this procedure is start by using large amounts of infectious viruses. Viruses like particles vaccine from coronavirus structure empty virus shells that are non-infectious. Five organizations are functional on virus like particles vaccines; this can produce strong immune response [83].

9. OTHER THERAPEUTIC INTERVENTIONS

AbCelleraA total of more than 500 specific antibodies from sera in the awareness of a COVID-19 patient have been noticed by this Canadian biotech and developed solely human IgG1 mAbs treatment for coronavirus infections in collaboration with Eli Lilly. Nano Viricides These is created by a different approach with the virucidal Nano micelles attached chemically to the S protein. Community testing is still on-going [84]. Apeiron Biologic The recombinant protein strategy is employed by the design of the

ACE2 recombinant (APN01) enzyme, which makes them bind to circulating virus particles that are refractory when entering the cells [85]. The SARS-CoV-2dangerous outbreak in Wuhan and other countries of the world causes hundreds of deaths, there is a significant need to reduce the person to person transmitting of the virus. And also, there is a need to provide awareness about disease symptoms, testing, and treatment to people. Health advice people would know about its signs because its symptoms are similar to influenza so people with influenza should have to take care of their selves. Govt of the country would give health advice to people as people who are infected with influenza or have a severe respiratory problem would concern doctors and don't make contact with healthy persons. Like when an outbreak of SARS occurred, WHO established networks to prevent infection, including more than 800 CDC employees working to provide health advice to people SARS-CoV-2 testing efficient treatments, medications, and vaccines are urgently needed. There are already several experimental diagnostic platforms in use in China and elsewhere. Virus testing would be present in each city of each country so that the general population would access to testing and also a mode of testing would be cheap. In every country around the globe, WHO would design a yearly roster of testing in order to reduce the transmission and the amount of deaths Rate of SARS-CoV-2 transmission 2.2% but it spreading very rapidly outside the Wuhan and it is predicted that like MERS and SARS super-spreader will be increased in the near future so there is a critical need of virus testing and treatment. Self-protection people infected with influenza would use a mask and they would not touch unwashed hands to mouth or eyes. People would take care of their selves in changing seasons; they would not go to crowded places. As CDC has mentioned some protective measures to avoid this use more amount of water in your daily need and eat properly cooked food. Restrict visitors from entering the SARS-CoV-2 patient's room. Advise travellers to avoid contact with animals and to other locations where they have been identified as infectious. Programmatic need to reduce transmission the government of every country should play a part to lessen its transmission rate by establishing different NGOs and these NGOs should have different teams that make surveys in the infected sections of the country in direction to instruct the people with the hostile effects of this virus on human body and to give them alertness on 2019n-CoV from every aspect. During the SARS outbreak and control predicted that at the global and local level workshop should be performed to inform people about SARS this will reduce the transmission of the virus as the SARS outbreak was control in this way. A clinical trial to minimise transmission is now underway. There are presently no clear antiviral medications for COVID-19, and the main therapeutic alternatives for COVID-19 are beneficial clinical trials. China conducted a clinical trial to show that Remdesivir and Chloroquine are useful towards SARS-Cov-2Cthat kind of clinical trial would be promoted. Also, the WHO and CDC will make an effort to develop their vaccines. Chinese authorities said that are ready to provide treatment to CoVID-19 infected patients around the world. In November 2003 SARS outbreak occurred in

China and authorities controlled this virus and China had performed its role with the CDC team to eradicate viruses all around the world.

10. CONCLUSION

The current information on SARS-CoV-2 pandemic is discussed in this paper. We also review possible therapeutic approaches currently being studied and potential outlooks for the disease in moreover to a description of epidemiological, clinical and radio-logical characteristics of SARS-CoV-2. The new clinical trials began quickly at the start of the pandemic emergency, currently being performed are explanations. Many of them depend on repurpose of previously developed therapeutically cause for other uses. The following agents can be isolated into two broad categories: those focused on immunotherapy, which can specifically target the viral replication process, and which either improve the inborn antiviral immune response or mitigate the harm caused by deregulated inflammatory responses. Whereas the common target SARS-CoV-2 is also tested for vaccines and therapeutic antibodies, this approach would be longer in length because it needs rigorous safety testing. SARS-CoV-2 has certainly caught the world's attention early in 2020, posing a significant threat to public health systems and current antiviral strategies. We assume that this could cause more systemic strategies to prepare us for future pandemics in advance. More systematic methods in the time of big data can be used to classify possible drug re-purposing.

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12. CONFLICT OF INTEREST

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

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14. REFERENCES

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