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Review Article

Repurposed Drugs and Alternate Therapeutic Possibilities for Challenges Posed By Covid-19

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A B S T R A C T

Pandemics like SARS-CoV-2 and its associated illness named COVID-19 (coronavirus disease 2019) have become a regular occurrence in the past recent decades. Though, novel Coronavirus devastated human lives, its earlier cousins SARS-CoV1, MERS and lesser known infections like 229E, NL63, OC43, HK01 were less threatening. Humankind should brace up towards identifying, managing and finding a suitable cure to prevent incidence of such deadly diseases. It is a well-known fact that viral diseases can be curbed only with vaccines. In this respect, the world has witnessed both the design and delivery of vaccines against SARS-CoV2 in a record time. Candidates for Vaccines designed vary from targeting proteins or nucleic acids (DNA and RNA) of the virus, with or without adjuvants with a potency to generate memory. Though, this has been lauded by the entire humankind, there is still the need for other therapeutics to control and treat COVID-19. Therapeutic Drugs are inexhaustible group of molecules that showed some promise in diagnosis, treatment or prevention of SARS-CoV-2 but provide no form of 'memory'. In this Review, we summarize the current knowledge on the therapeutic options other than vaccines or licensed antiviral drugs that can be repurposed to be considered for the treatment and prevention of the SARS-CoV-2 virus.

Keywords: SARS-CoV-2, Therapeutics, Drug Repurposing, Pharmacophores, Antivirals, diagnostics

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INTRODUCTION

Humanity has been ravaged by diseases and illnesses since time immemorial. Owing to exotic trade routes, humans live in large clustered cities, and encounter increased contact with different populations of people, animals and ecosystems. Thus, the scale and spread of these diseases have increased dramatically due to the marked shift to agrarian communities. It has been observed that the previous severe acute respiratory syndrome coronavirus (SARS-CoV) caused five times lesser fatality rate than Middle East respiratory syndrome coronavirus (MERS-CoV). Whereas, SARS-CoV-2 is more aggressive than genetically very similar SARS-CoV-1 and shares 86% of the same genomic sequence, yet the former is lethal[1]. Recently, it has been revealed that the SARS-CoV-2 is about 96% similar to RaTG13 virus at the nucleotide sequence level which originated from horseshoe bats (Rhinolophusaffinis)[2]. The double positive (+) sense single stranded RNA of SARS-CoV-2 makes frequent mistakes in copying resulting in high incidence of mutations and that can be the reason that SARS-CoV-2 has disastrous consequences on the new host. Of all the 116 mutations described so far, the three most common mutations which might affect the severity and spread of the SARS-CoV-2 are 8782C>T in ORF1ab gene, 28144T>C in ORF8 gene and 29095C>T in the N gene[3].

India is recently grappling under the second surge of SARS-CoV-2, aptly quoted as the "tsunami of pandemic" by worldwide media as it continues to break records in caseloads as well as death counts. Many experts are hinting towards the "triple mutant strain" or "triple mutant variant" of coronavirus as one possible reason for the uptick in India's cases. However, Indian scientists leading the Indian SARS-

CoV-2 Genomic Consortia (INSACOG) at the Centre For Cellular And Molecular Biology argue that the "Triple Mutant" is a misnomer as this particular B.1.617 has already had 13 mutations but notably gathered three very conspicuous mutations that might have increased its transmission ability or given it an edge to evade the immune system. Over the past one year, in India itself, approximately 24,300 mutations are detected in 7,000 variants of the SARS-CoV2 that are currently under circulation.

Although extensive work is being carried out worldwide to understand the molecular mechanism and the disease pathogenicity of SARS-CoV2, still the underlying mechanism has many nuances to unravel. Thus, designing and development of appropriate therapeutic drug or a vaccine to combat COVID-19 is extremely challenging. Though vaccines against SARS-CoV2 are claimed to work well against all the emerging variants, there is a need to rapidly develop other alternate therapeutics against such emerging viral diseases. In today's time scientific technology like the understanding of the virus genomics and structural biology has paved the way for multifaceted approaches to identify the correct candidates for drugs against COVID-19[4]. Though, vaccines have proven to be potent against COVID-19, other therapeutic Drugs have also showed some promise in diagnosis, treatment or prevention of SARS-CoV-2. Vaccines definitely have the ability to impart "memory "in the form of T-cell activation, but these inexhaustible groups of small molecules should be explored as 'immunity boosters' albeit with no form of 'memory'. This review comprehensively lists such therapeutic drugs to be considered because till date there are no potential drugs to cure COVID-19.

PLAUSIBLE THERAPEUTICS FOR SARS-CoV-2

For the last three decades, in-silico utilities based on conformational optimizations and target space sampling strategies were found to be very effective in accelerating the conventional drug designing process. The algorithms for receptor modeling, binding affinity estimation through docking scores, system behavior simulation, and analysis through molecular dynamics studies are being instrumental in the fastest prediction of the fate of small molecules on the target receptor. Similarly, various spatial statistical features-based models (pharmacophore) and mathematical models like Quantitative structure–activity relationship models (QSAR) and Quantitative structure–property relationships (QSPR) are crucial in the process of drug discovery[5]. These days all of the above-said strategies have been used together to test and validate the effective usage of known molecules (approved or investigational drugs) on novel receptor targets with a lower risk of failure and avoidance of clinical trials. Thereby, saving time and expenses required for the human trials in launching new drugs and avoiding legal procedures before commercialization and human applications. This process of computational drug repurposing offers a unique advantage of faster identification of potential therapeutics.

Similar strategies have been implemented by various researchers across the globe for Human Coronavirus (HCoV) by screening the existing repertoire of drugs and by targeting the essential enzymes required for viral replications and transcription in HCoV. Structure and pharmacophore-based screening backed by molecular dynamic analysis have been opted to find out effective therapeutics, which could serve as potent inhibitors of an array of viral protein targets in HCoV[6]. The entire genome of SARS-CoV-2 was sequenced on 11 January, 2020 and was available to the world for research on Coronavirus[7]. Real time statistical data is now being available that helps the scientist track the evolution of this virus and the mutations to its various strains. Nearly 500 clinical studies are carried out worldwide on the development of therapeutics candidates apart from vaccines for COVID-19 which are registered with the World Health Organization Clinical Trial Registry[8, 9].

Therapies targetting the non-structural and structural proteins of sars-Cov-2

Armed with ~ 29,829 base pairs, the viral genome of HCoV encodes around 29 proteins which include 16 non-structural proteins and four main structural proteins namely spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins (**Figure 1**). Strategies that target each of the structural and non-structural proteins are the new therapeutic approaches.

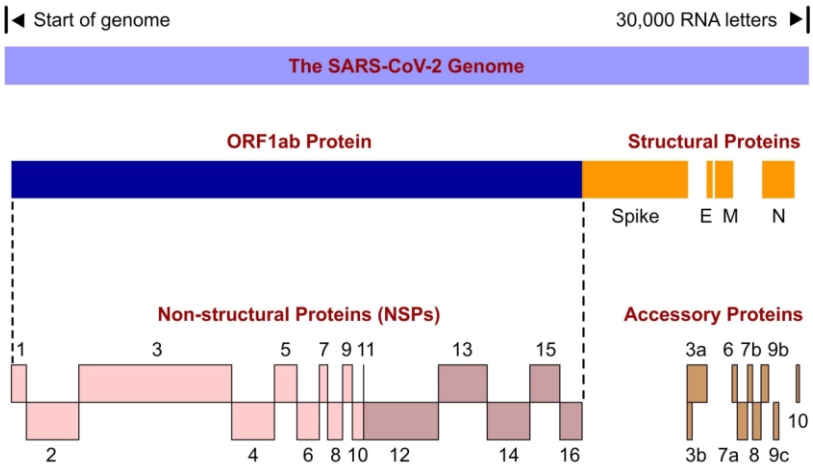

Figure. 1: The genome structure translating the proteins for the Novel Coronavirus RNA.

Envelope Protein

The E protein is the smallest structural protein (75aa) of HCoV, which is composed of a hydrophobic domain and the charged cytoplasmic tail. It has a special role in viral morphogenesis and acts as a virulence factor. E protein function as an ion channel required for the pathogenesis of SARS-CoV and probably also of SARS-CoV-2 [10]. The importance of E protein in viral assembly and budding makes it a target for antiviral therapy [11]. However, due to the lack of conservation among interspecies domain, this protein is yet to be considered as a promising drug target [12].

Membrane Protein

The M protein maintains the shape of the viral envelope and is crucial for stabilizing the nucleocapsid protein[8].This protein is characterized by three TM domains and plays an essential role in facilitating multiple protein-protein interactions needed for the viral assembly and replications[11].While maintaining the overall structural similarity, different coronaviruses show diversity in their amino acid sequences[12].Both the nuclear factor kappa pathway and IFN-beta pathways are activated by the M protein of SARS-CoV[13]. These properties are explored for the development of vaccines against SARS Coronavirus in mice and SCID-PBL/hu mice, where mice vaccinated with SARS-m DNA showed good T-cell immune response[14].

Nucleocapsid protein

The Nucleocapsid protein (NP) is one of the most abundant proteins in coronaviruses commonly involved in the RNA binding, replication through EF1α-mediated action, transcription, and viral genome packaging. It is composed of three domains with the N proteins binding to the viral RNA through its RNA-binding domain (RBD) of about 140 amino acids[11].It is highly immunogenic and has a conserved pattern of amino acid sequences, making this protein a prominent candidate for vaccine discovery and development of diagnostic assays. One candidate molecule designed for this target is N-(6-oxo-5,6-dihydro-phenanthridine-2-yl) (N,N dimethylamino) (PJ34), which affects the genome binding and replication process of CoV[13].The RNA binding site of nucleocapsid protein has been used to design an inhibitor 6-chloro-7-(2-morpholin-4-yl-ethylamino) quinoxaline-5, 8-dione (small-compound H3), which reported a significant decrease in RNA-binding capacity of NP by more than 20% [15].Some of the herbal products rich in polyphenolic compounds have shown inhibitory action against SARS-CoV.

Spike Protein

The spike protein is a clove-shaped transmembrane protein with the membrane fusion subunit (MFS) and receptor-binding domain (RBD) protruding out of the surface, giving it the appearance of a crown (a contrasting characteristic in all Coronavirus species)[16,17]. The spike protein of HCoV plays an important role in virus entry into the host through interactions between the RBD and host ACE2 receptor, which allows the CoV- RNA genome to enter the host cells. The species specificity and tissue tropism of the virus are determined by the interaction between the S protein and its receptor[7]. Few studies were reported that target the RBD by small peptide sequences through peptidomimetic strategies[13].Eighteen small molecules facilitated S-ACE-2-mediated targeted entry of the virus into human cells; while inhibitors like SSAA09E2, SSAA09E1, and SSAA09E3 prevented fusion of host and viral cell membranes. The much-discussed Chloroquine, an antimalarial agent interferes with the virus receptor binding. Hence, this protein is an important target for structure-based drug designing.

Hemagglutinin esterase

The Hemagglutinin esterase (HE) is an envelope-associated protein that is reported to be expressed only in certain specific strains of CoV (beta-CoVs). The HA protein is synthesized as an inactive precursor (HA_0) and its cleavage into HA_1 and HA_2 subunits by a cellular protease mediates binding of the virus to the host cell receptor. Serine protease inhibitors like e-amino caproic acid and Nafamostat have been reported as inhibitors for HA_0 and thus blocking the viral infection in both cell and animal models. Arbidol was also found to stabilize HA_2 and was helpful in the prevention of acidification-induced reconfirmation of HA_2 [18].

Proteases

The replicase gene is a major component of the HCoV genome, which encode 16 non-structural proteins (NSPs) in the form of two polyproteins (PP). Two types of cysteine proteases, Main Protease (Mpro) and papain-like protease (PLpro) act on these PPs to release the NSPs[19].The viral replication is facilitated by the main protease (Mpro), which is currently the most popular target for the design and discovery of small molecules-based therapeutics through drug repurposing. Viral enzymes such as the helicase and two cysteine proteinases that are mainly involved in the important cellular processes like the replication, transcription, and/or post-translational polyprotein processing are being considered as targets against COVID-19. Using in-silico high-throughput screening approaches, inhibitors in small molecules like arylboronic acids, quinolinecarboxylate derivatives, thiophenecarboxylate, and phthalhydrazide-substituted ketoglutamine analogs have shown to be potential inhibitors for these enzymes[20]. Further, metal-conjugated and peptidomimetic compounds showed inhibitory activity against 3CLpro. N-(benzo [1,2,3] triazol-1-yl)-N-(benzyl) acetamido) phenyl) carboxamides and ML300 are also found to be important inhibitors of CLPro. Many commercially available drugs like bepotastine, colistin, valrubicin, icatibant, vapreotide, caspofungin, epoprostenol, epirubicin, perphenazine and aprepitant act as inhibitors for the active site of HIV protease (Mpro). Though among these, only Lopinavir and ritonavir are explored as protease inhibitor and are being used in the treatment of COVID-19[13]. Flavonoids and higher doses of zinc are also noted to inhibit both types of SARS protease (CLpro and PLpro)[13].

Repurposed drugs as therapeutics against covid-19

Effective drugs for COVID-19 have still many milestones to reach, though vaccines have hit the market and are available for human use. Apart from the cure for COVID-19, many investors and researchers are developing the alternate options

with repurposed drugs or medications to treat symptoms and control the virulence. Clinical trials for SARS-CoV-2 virus to identify other host proteins are being considered as targets by existing drugs. The studies are in nascent stage as complete pharmacoepidemiology needs urgent attention regarding their usage in real life conditions, interactions between drugs and human populations, their benefits as well as risks associated of these proposed drugs[21]. Efforts are made in the direction to target host-virus interface, which had less probability for mutations, to be used as a durable broad spectrum treatment regime. Drug repurposing or drug repositioning is a strategy of investigating approved drugs or drugs under investigation for new therapeutic uses that are outside the scope of the original medical use[22]. Thus, small molecule candidates for host-directed therapies should be the new mantra for dealing with SARS-CoV-2 infection and more than 300 such molecules are registered as possible therapeutics for COVID-19[23]. New formulations and combinatorial drugs must be explored by pharmaceuticals but it should be ensured that they should not be given in practice freely for the treatment or prevention of COVID-19 unless they are thoroughly researched. Thereafter, Pharmacies should not only explore new drugs but also should ensure supply chain and distribution of these drugs[24].Several drugs are being investigated to be repurposed as viable treatments for COVID-19. They comprise not only antivirals, but also antimalarials, antibacterial, anti-inflammatory drugs, and antipyretics. Also other therapeutic approaches are being explored that comprise of vitamins, herbal medications, Convalescent therapy etc.

Antiviral drugs

Nucleotide analog. Evidences showed that Remdesivir, a monophosphate prodrug and a nucleotide analog (GS-5734) has potent antiviral activity against several viruses like Ebola, SARS, and MERS, both *in vitro* and *in vivo* [25, 26]. In *in vitro* experiments, low micromolar concentration of Remdesivir was found to be effective against SARS-CoV-2. Similarly, patients' administered with Remdesivir showed drop in fever with improvement in clinical symptoms like lesser chest infiltrations and negative result by the 12th day of illness[27]. Remdesivir is metabolized by the host into active nucleoside triphosphate that disrupts the viral genome replication process by inhibiting RdRp, the complex that controls replication[28]. It also has the ability to bypass the proofreading tendency and increased viral fidelity of CoV2, thus making it an efficient antiviral agent [29]. However, more clinical evidences are needed to confirm its efficacy and safety[30].

Recently, Cidofovir Anhydrous which bears structural similarity to nucleotides (acyclic nucleoside phosphonate) and is approved for treatment of HCMV retinitis, presents as an important repurposed antiviral drug by competing with deoxycytosine-5-triphosphate (dCTP) and blocking viral DNA replication[31]. Another prominent antiviral drug Umifenovir (Arbidol) which works against many viruses including influenza A, B, and C, respiratory syncytial virus (RSV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), adenovirus, parainfluenza, poliovirus, rhinovirus, coxsackievirus, Zika virus, hepatitis B and C viruses has been repuposed for the tretment of COVID-2 [32].

Nucleoside analog.

Nucleoside analogues target RNA-dependent RNA polymerases (RdRp) and block viral RNA in a broad spectrum of RNA viruses, like human coronaviruses[33]. Favipiravir is an approved nucleoside analogue present in the form of adenine or guanine derivative and is known for broad-spectrum inhibitor of RdRp. Favipiravir treatment showed inhibitory action for viral RNA polymerase and replication in patients with Ebola and Influenza[34]. In the year 2014, Favipiravir was approved in Japan, and recently Shenzhen Health Commission also approved it for the treatment of COVID-19 patients[35]. Similarly Ribavirin, also a possible nucleoside analog, showed potent antiviral activity against hepatitis C virus, respiratory syncytial virus, some viral hemorrhagic fevers, and SARS[36]. Ribavirin suppresses formation of guanosine triphosphate thus inhibiting replication of both DNA and RNA viruses. Although, ribavirin was noted to deplete haemoglobin count hence can be dangerous to patients with respiratory distress. Thus, undesirable effects of ribavirin must be nullified before it could be considered as a possible candidate therapy for the treatment of COVID-19 patients.

Protease inhibitors. A combination regime of Ritonavir and Lopinavir is used in HIV patients as a well-known protease-inhibitor to stop viral replication. Treatment with this combination has shown effectivity in ameliorating the respiratory distress syndrome in MERS and SARS patients[37]. Also, lopinavir/ritonavir combination along with interferon-1β treatment showed promising results in MERS-CoV infection[38]. Considering the similarity of SARS-CoV-2 to all other coronavirus, it can be speculated that this combination drug may bind to endopeptidase C30 of the SARS-CoV-2 protease and exhibit an antiviral effect in COVID-19[38]. On this basis, few clinical trials were performed for COVID-19, but regretfully, the results are not satisfactory[39]. However, some researchers were able to confirm the inhibitory effect of Lopinavir and Ritonavir at high concentration but further work is definitely required before it can be pronounced as a potential candidate for COVID-19.

Another group of HIV-protease inhibitors (PIs), Darunavir&Cobicistat are used to repurpose for COVID-19. *In-vitro* studies with the combination of Darunavir/Cobistat (DRV/c) at clinically relevant concentrations showed no antiviral activity against COVID-19 virus[40]. Another study conducted by Jun Chen and his team on 30 patients with mild COVID-19 revealed that five days of DRV/c administration was comparable to care alone, and was well tolerated[41].

SS2 is a serine protease that primes spike glycoprotein of human coronaviruses and enables host cell entry. TMPRSS2 is inhibited by Camostatmesilate (CM), as it is shown to block the pathogenesis and further spread of SARS-CoV into the lung cells of SARS-CoV-2 infected patients[42]. Japan is the first country to have approved its use for the treatment of postoperative gastric reflux and chronic pancreatitis.

Antimalarial drugs

Chloroquine (CQ) and hydroxychloroquine (HCQ) are developed from the bark of the cinchona plant and are known antimalarials as well in autoimmune diseases such as rheumatoid arthritis or lupus[43]. Though, many controversies were presented on its clinical validity, it has been proven to be effective in the treatment of COVID-19[44]. Additionally, in vitro results showed HCQ sulfate to be significantly superior to the CQ phosphate in inhibiting SARS-CoV-2[45, 46]. Both CQ and HCQ have structural similarity and hence follow the same mechanism of action. Both increases the pH of acidic endosomes/lysosomes and block the autophagosome-lysosome fusion[47]. A lowering of cathepsin level is seen that results in SARS-CoV-2 spike-protein cleavage due to the formation of autophagosome. Moreover, CQ inhibits p38 mitogen-activated protein kinase (MAPK) thus, altering the virion assembly. MAPK signaling leads to virus activation that subsequently result in their replication cycle[48]. On March 2020, HCQ was declared as a drug against SARS-CoV2 and subsequently United States Food and Drug Administration also approved of its medication. A combination therapy (HCQ and azithromycin) showed significant reduction of the viral load in the infected patients as compared to HCQ treatment alone. HCQ and azithromycin are being used for the treatment of COVID-19 patients with moderate to severe disease in many countries[49].However, prolonged use of HCQ and CQ can lead to fatal dysrhythmias, electrolyte disturbances, retinopathy, deficiency ofglucose-6-phosphatase, and corrected QT interval prolongation. Thus, there is not enough evidence regarding the efficacy and safety in the treatment of COVID-19.

Anti-bacterial drugs

Azithromycin is a macrolide antibiotic that is utilized to treat various kinds of bacterial infections including pneumonia, bronchitis, some sexually transmitted diseases, and certain infections. The use of Azithromycin has been sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). A positive outcome was obtained clinically from SARS-CoV-2 infected patients in a clinical trial using a combination of azithromycin and hydroxychloroquine[49]. Azithromycin usage in the treatment of critically ill patients with MERS, however, showed that there was no association between the Azithromycin therapy and the reduction of the 90-day mortality rate and there was also no improvement in MERS-CoV RNA clearance[50]

Anti-inflammatory drugs

Ruxolitinib is an inhibitor of Janus-associated kinase pathway (JAK1/2) and is popularly used against diseases such as myelofibrosis or polycythemiavera. It helps manage the hyperactive immune reactions of the host during diseased condition and also after transplant of bone marrow. It suppresses allergic and immune responses in the host. The patients who received Ruxolitinib showed significantly lower levels of 7 cytokines than the control group[51].

Baricitinib is a cytokine-release inhibitor, an anti-JAK (inhibitor of Janus kinase) and is used for rheumatoid arthritis treatment. It is very effective and has records of safety[52].Baricitinib is also an AAK1 (AP2-associated protein kinase 1) binding drug. AAK1 disruption interrupts the entry of the virus into cells while also interrupting the intracellular arrangement of the virus particles. It also coheres to a regulator of endocytosis, namely cyclin G-associated kinase[53]. A short study conducted by Cantini et al. [54]confirmed its safety in the clinical context with moderate COVID-19 pneumonia. The clinical and laboratory parameters were greatly boosted by Baricitinib therapy. Sponsored by the NIAID, the Adaptive COVID-19 Treatment Trial (ACTT-2) was undertaken to assess the viability of a combination of Baricitinib and remdesivir versus Remdesivir alone. The results indicated a reduction in the recovery time of hospitalized COVID 19 patients.

Dexamethasone is a type of corticosteroid and has potent anti-inflammatory and immunosuppressive properties. In a clinical trial conducted, patients that were under normal care and those that required ventilation in COVID-19 infection, administration of dexamethasone reduced deaths by one-third in normal care and by one fifth in only oxygen receiving patients[55].Parallel to dexamethasone, Glucocorticoids are also used to treat varied pulmonary inflammatory diseases. The initiation of the immune defence responses of the body is inhibited by early treatment with glucocorticoids. Curbing the immune system usually leads to increased viral load leading to adverse consequences [56] and thus it is used mainly in the treatment of critically ill patients those suffer from cytokine storm[57, 58]. A study conducted in COIVD-19 infected adults by Lu et al.demonstrated that neither lung inflammation duration nor mortality rate was reduced by the use of systemic glucocorticoid, however, the duration of fever was reduced significantly[58].

Tocilizumab (TCZ) is a monoclonal antibody against interleukin-6 (IL-6) that can be effective to limit SARS-CoV-2 pneumonia with acute respiratory distress syndrome (ARD) or a hyper-inflammatory syndrome. Administrating Tocilizumab either intravenously or subcutaneously in patients with severe SARS-CoV-2 pneumonia (TESEO) reduced the invasive risk of mechanical ventilation or death[59].Moreover, the response to TCZ was sustained, rapid and notable clinical improvements were seen [60].

Antipyretics and Pain relievers like ibuprofen, naproxen, and diclofenac are administered to patients with acute respiratory-tract infection which may have the danger of myocardial infarction, heart failure, and stroke. The worsening situation was seen wherein ibuprofen administration increases the binding of corona viruses to ACE2 and can increase its bioavailability[61,62]. Furthermore, NSAIDs are highly nephrotoxic and was shown to worsen the clinical manifestation in COVID patients[63, 64]. Hence, the role of antipyretic in COVID-19 patients is debatable in light of the harmful side effects of ibuprofen in patients with COVID-19. In such a scenario, use of acetaminophen along with ibuprofen for fever reduction in a patient with COVID-19 is preferred[65].

Other therapeutic approaches

Herbal formulations.A large section of population in the South Asian countries including China, and India rely on traditional medicines for treatment of various diseases [66]. In

the quest for effective drugs against COVID-19, many traditional Chinese medicines have gained much popularity. Among those are herbs like Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikoviae Radix (Fangfeng), Lonicerae Japonicae Flos Astragali Radix (Huangqi), Atractylodis Macrocephalae Rhizoma (Baizhu), and *Fructus forsythia* (Lianqiao)—have shown some effective role in the prevention and control of COVID-19[67]. However, most of these herbal candidates still await extensive research and clinical trials before they are actually used as COVID-19 medication[67, 68]. Similarly, a large number of potential Indian herbs and medicinal plants (Glycyrrhizaglabra, Allium sativum, Strobilanthescusia, Acacia nilotica, Eugenia jambolana, Euphorbia granulate, Ocimum sanctum, Solanum nigrum, Vitexnegundo, Oci-mumkilim, and Scharicum) have been elucidated as potential drug targets in the prevention of SARS-CoV, HCoV, and HIV[69, 70]. Our group has also recently published an article elucidating the role of Cucurbitacins as the potential herbal medicine against COVID-19 [71].

***Vitamins*.** It has always been a popular practice to have dietary supplements of Vitamin C and D to boost our immunity. Both these vitamins are worthy supplements known to suppress viral replication rate and are usually given to patients suffering from influenza. Subsequently a daily of dose of vitamin C (2–10 mg/day given over 8–10 h) provided to severe and moderate COVID-19 patients did cure and even got them discharged[72]. Simultaneously a dose of 10,000 IU/day of vitamin D3 was shown to raise the 25 (OH) D serum concentrations in COVID patients.

Along with Vitamins, Zinc supplements are also recommended as therapeutic or prophylactic program for treating COVID-19. Zinc has the capacity to have antioxidant and immunomodulatory properties, thus was shown to manage many viral diseases such as influenza, rhinovirus, and coronaviruses [73].

Monoclonal Antibodies are laboratory-made variants of immunoglobulins normally synthesized by the humoral branch of immune system on encountering pathogens or any foreign entity. Neutralizing antibodies, monoclonal or natural, can prevent virus infection in the cell by binding directly to portions of viral epitopes that binds to ACE2 receptors. Short term protection can be provided by the use of monoclonal antibodies against SARS-CoV-2.

Convalescent Plasma Therapy(CPT) is used when the antiviral antibodies are transferred via plasma transfusion from potential donors to the patients. High convalescent antibody titre to COVID-19 was associated with the absence of myalgia, advanced age, blood type, fatigue, fever, and hospitalization. 80% of patients treated with CPT displayed a notable increase in post-transfusion antibody levels, in spite of the variance in donor titre [74]. It was shown that the condition of 70% of the patients who had severe respiratory symptoms improved and oxygen supports were removed within 7 days after CPT with a significant decrease in viral loads and C-reactive protein (CRP) concentration and an increase in the percentage of lymphocytes. Another study with 25 patients found that the therapy was well-tolerated, with no adverse side-effects that are observed related to the transfusion[75]. That is the world's first Randomised Control Trial for Plasma therapy that was completed, it showed faster clearance of viral load, improved oxygenation, and improved symptoms in the patients[76]. However, the PLACID (PLAsma Convalescent InDia) trial conducted by the Indian Council of Medical Research (ICMR) has shown that severe disease or death could not be forestalled by the use of convalescent plasma in the COVID-19 patients.

Low Dose Radiation Therapy (LDRT) is reported that fatal COVID-19 cases are usually fast progressive and treatment via anti-inflammatory is of utmost importance to curb the raging immune responses within the body. Usually, a COVID-19 patient deteriorates within 2 weeks after the onset of the disease due to the extensive release of proinflammatory mediators, which is prevalent in critically ill COVID-19 patients [77]. Therefore, prompt initiation is essential to obtain the desired outcomes of the treatment [78]. Molecular mechanisms involved in inducing anti-inflammatory effects are being used to treat patients with pneumonia using Low Dose Radiation Therapy (LDRT)[79, 80]. However, LDRT did not show any considerable decrease in cytokine storm [81], as it is generally used to decrease inflammations that are limited to diseases such as osteoarthritis. Thus, cytokine storms in COVID-19 may not be controlled by the use of the anti-inflammatory effects of LDRT. A major concern with its usage is that the immune response against infections is suppressed that could cause a delay in the elimination of the COVID-19 virus[82].

CONCLUSIONS

Several viruses, including the new one, have made the jump from animals to humans by mutation, but most just cause cold-like symptoms infecting mainly the respiratory tract. But viruses that cause diseases like SARS, MERS, and COVID-19 are lethal[66]. COVID-19 is closely related to SARS that swept the world during 2002-03. Though, it was easy to contain it as those infected showed immediate severe symptoms and were isolated, so it was easier to identify them to control. The other related corona virus disease, the Middle East respiratory syndrome (MERS) emerged in 2012. COVID-19 is different from SARS and MERS as the spectrum of the disease is quite broad. In 80 per cent cases, it leads to mild infection or no symptoms. Only a test can confirm the presence of the virus. All such corona-positive people with mild or no symptoms become the carrier of the disease. This makes the control of the disease more difficult. From the evolutionary perspective, SARS-CoV-2 turns out to be much smarter than its other cousins like SARC-CoV-1 by having some morphological and physiological advantages which make it fitter for survival[83]. The newly designed vaccines are putting more evolutionary pressure on these viruses to change, to reproduce faster and spread easily to new hosts. Whether it is an emerging epidemic scenario like COVID-19 or a future epidemic, epidemiological models are therefore very useful. Tools to assess the intervention strategies for disease control, both for short and long term. Humanity is fighting this pandemic at many levels as there is still no cure yet for COVID-19. The second wave has ravaged across the countries and caused immense loss to humanity. As medical professionals struggled with the right treatment regimens for covid-19 patients, it took almost a

year to draw certain guidelines in using over-the-counter available drugs. The latest guidelines issued by central health ministry along the lines of WHO are based on evidence-based treatment for COVID-19 patients and recommended only four repurposed drugs (Remdesivir, Steroids, Anticoagulants and Tocilizumab) for moderate to severe patients. Thus, the therapeutics options that should be considered: (i) Gaining better understanding of this virus and carrying out research aimed at developing a vaccine; (ii) Manufacturing enough test kits; (iii) Ensuring there is no shortage of the necessary medical equipment; (iv) Finding ways to contain the transmission; (v) To find appropriate drugs either from natural resources or via repurposed strategy, and Lastly, (vi) Raising awareness.

CONFLICT OF INTEREST

The authors have no financial support from any grant or the Institution. All the authors declare no 'Conflict of Interest'.

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