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Review Article

Complementary/Alternative Medicine Section

Vaccines, Repurposed Drugs and Alternative Biomedicines for the Management and Prevention of COVID-19

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ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) popularly called as COVID-19, is a pandemic having affected >200 countries. Globally, quarantine measures have been implemented to slow down the spread of the virus. Yet, the available vaccines and drugs for treating COVID-19 are still in design and developmental stage, requiring clinical validation. This review is focused on the progress in the development of medicines against SARS-CoV-2. As an alternative approach, both conventional and traditional biomedicines are also reported to be in practice, to treat the SARS-CoV-2 infected patients. Considering the therapeutic values of the folk medicines, this review focuses on the usage of high value added products from plants, against COVID-19 in managing the symptoms like fever, cough, cold, sore throat, respiratory disorders and kidney dysfunctions enlisting a few used since time immemorial. It is ardently hoped that scientific intervention of such traditional plants can be integrated to harmonise with modern medicine, to ensure its dosage and safety in augmenting disease management.

Keywords: Antibody vaccine, Coronavirus disease 2019, Recombinant vaccine, Traditional medicine

INTRODUCTION

Novel coronavirus, SARS-CoV-2 (COVID-19) a spillover zoonotic virus, has evolved into a pandemic strain infecting human beings leading to fatal respiratory illness [1]. The whole genome sequencing of this crown shaped virus (WIV04 strain) is identified as the Beta-coronavirus 2B family. It has 82% sequence similarity with SARS-CoV Tor2, 88% with bat SARS-like coronavirus and 96% with bat-SARSr-CoV RaTG13 [2]. Apart from the presence of SARS-CoV proteins such as nucleocapsid protein (N), membrane glycoprotein (M), and spike glycoprotein (S)(3), the special protein that makes COVID-19 more infectious could be the presence of glycoprotein having acetyl esterase and haemagglutination (HE) properties. Currently, there are five variants of the virus which have been first identified- B.1.1.7 (UK), B.1.351(South Africa and US), P.1 (US), B.1.427 and B.1.429 (California, US).

Based on the symptoms, the clinical manifestation of the infection is divided in to five different stages. Stage I is asymptomatic but positive, stage II-positive with mild upper respiratory symptoms like sore throat, dry cough, sneezing, nausea, vomiting, and diarrhoea [4], stage III is an initial stage of pneumonia with chest tightness, fever [5] and palpitation [6], stage IV with an Acute Respiratory Distress Syndrome (ARDS) requiring oxygen therapy, and stage V associated with chronic respiratory distress, kidney failure, septic shock, leading to multiorgan failure and death [8]. After the discovery of mutant strains of SARS-CoV-2, information about the characteristics of these variants in causing severe illness and symptoms leading to complications are under investigations.

Inimitable molecular mechanism of infection in the host cells, and the emerging mutant variants of coronavirus is a challenge for the available antiviral vaccine or therapeutics. Symptomatic and asymptomatic infection can provide herd immunity, which could be only on exposure to the virus.

VACCINE DEVELOPMENT AGAINST COVID-19

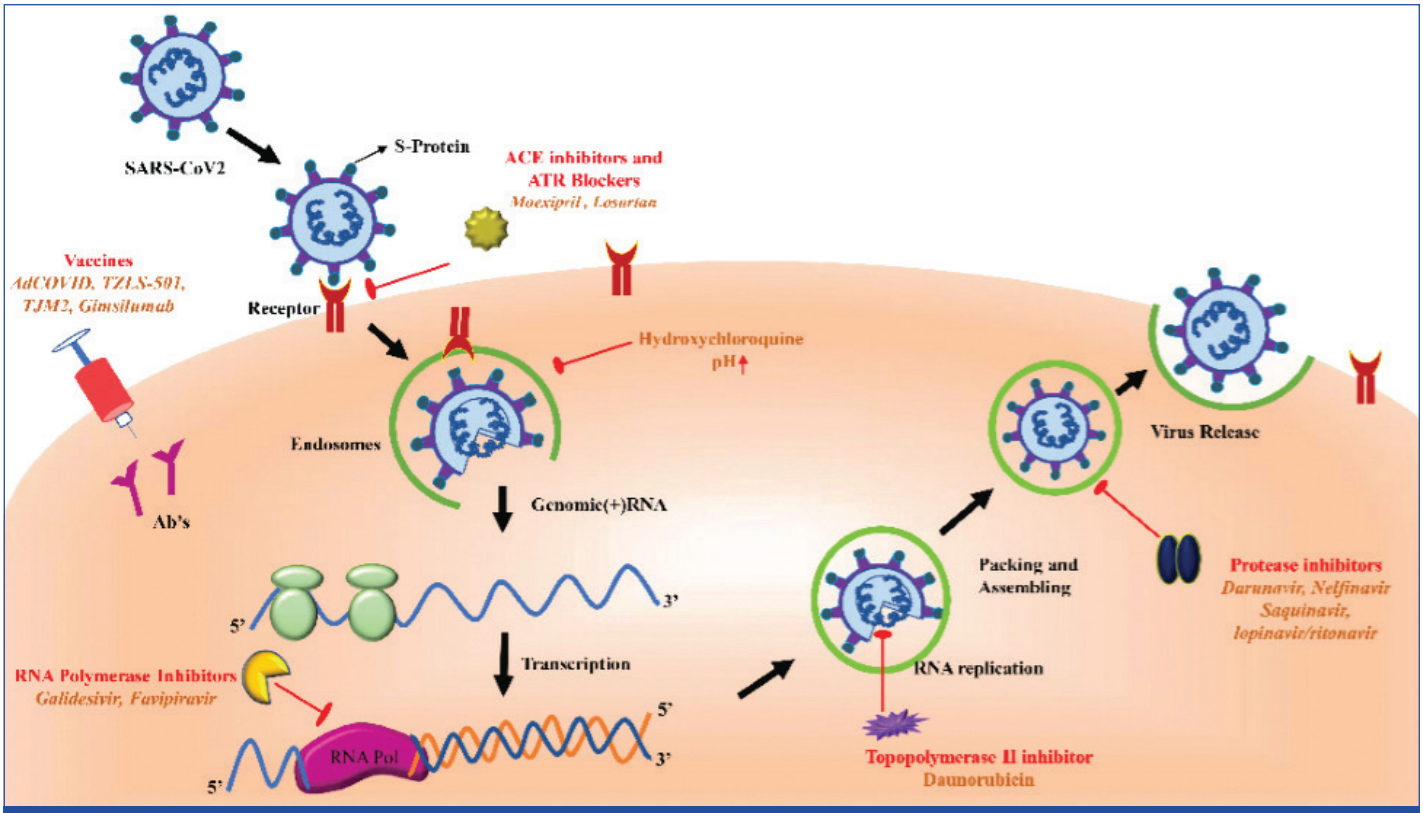
Vaccine for COVID-19 is in preliminary stage and almost 30 different vaccines are being developed in breakneck pace. They fall into four different categories of vaccines, such as Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) based vaccine, Antibody based vaccine, Recombinant vaccine and other vaccines which include inactivated vaccines [Table/Fig-1].

1. DNA and RNA based Vaccines

The first human trial for COVID-19 vaccine, Fusogenix DNA vaccine [9] was developed in Seattle, United States of America. It is a Proteo-Lipid Vehicle (PLV) formulation developed by Entos Pharmaceutical, which uses plasmid DNA containing multiple protein epitopes from crucial immunogenic SARS-CoV-2 proteins. This platform applies a novel fusion mechanism to deliver its genetic payload directly inside the cells. Another DNA vaccine, INO-4800 [10], is used for activation immunotherapy, developed by Inovio pharmaceuticals in collaboration with Beijing Advaccine Biotechnology. A smart device called CELLECTRA® delivers the optimised DNA into cells, where it gets translated into proteins that activates an individual's immune system to generate a robust targeted T-cell and antibody response. A parallel, phase one clinical trial is planned to be conducted in China, by Beijing Advaccine. The RNA based vaccine, mRNA-1273 [11] targets against SARS-CoV-2 encoding for a prefusion stabilised form of the spike (S) protein. ModernaTX, Inc, begins the phase I clinical trial of mRNA-1273 with three dose levels (25, 100 and 250 µg) on a two dose vaccination schedule, with a gap of 28 days and currently, it has been approved for human use. The miRNA-1273 inhibits the severe illness caused by COVID-19 infection with the efficacy rate of 94.1% [Table/Fig-2]. Comirnaty (BNT162b2), another approved vaccine has been developed by Germany-based BioNTech proprietary mRNA technology and co-developed by BioNTech (Germany) and Pfizer (Belgium). It is a nucleoside modified RNA formulated in lipid nanoparticles encoding an optimised SARS-CoV-2 full length spike protein antigen. Food and Drug Administration's Emergency Use Authorisation (EUA) has expanded its usage to include people of 12-year-old [Table/Fig-2] [9-12].

2. Antibody Based Vaccine

Kevzara, a fully human monoclonal antibody [13], is in phase two/three clinical trial in patients with severe COVID-19 infection. A



[Table/Fig-1]: Therapeutic implication of vaccine and drug against COVID-19.

Name of the vaccine	Stage of development	Type of vaccine	Mode of action	Name of the company	Ref
Fusogenix	Developing an optimised payload	DNA vaccine	Plasmid DNA containing multiple protein epitopes from crucial immunogenic SARS-CoV-2 proteins, stimulating an immune response in the body to prevent COVID-19 infection	Entos Pharmaceutical, Inc.	[9]
INO-4800	Phase II/III	DNA vaccine	CELLECTRA platform for the activation immunotherapy	Inovio Pharmaceuticals, Inc. in collaboration with Beijing Advaccine Biotechnology Co., Ltd.	[10]
miRNA-1273	Approved vaccine	mRNA vaccine	It act's against SARS-CoV-2 encoding for a prefusion stabilised form of the Spike (S) protein	Moderna Inc., and the Vaccine Research Center, USA.	[11]
Comirnaty (BNT162b2)	Approved vaccine	mRNA vaccine	Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2	Pfizer, Puurs, Belgium BioNTech manufacturing GmbH, Mainz, Germany.	[12]

[Table/Fig-2]: DNA and RNA-based vaccines for COVID-19 [9-12].

passive vaccine, REGN3048-3051 [14] developed by Regeneron, is prepared by a cocktail of mouse antibody and COVID-19 recovered patient antibody. It was approved to treat rheumatoid arthritis that could block the Interleukin-6 (IL-6) pathway. Another vaccine named, AdCOVID, Intranasal COVID-19 vaccine [15], is being developed by Altimmune on a vaccine technology platform. It is similar to NasoVAX, an influenza vaccine, and it is being tested to validate its immunological response against COVID-19 infection. The EpiVacCorona (DB16439) developed by Vektor State Research Center of Virology and Biotechnology in Russia is a chemically synthesised chimeric peptide vaccine that contributes in developing immunity against SARS-CoV-2 infection following two intramuscular administration spaced 21-28 days apart [Table/Fig-3] [13-19].

3. Recombinant Vaccine

Vaxart's VXA-CoV2-1, an oral recombinant vaccine, is based on the published genome of COVID-19 and tested in preclinical models for mucosal and systemic immune responses. It targets both the spike protein (S) and nucleoprotein (N) and triggers mucosal immune responses in humans. Interestingly, Clover Biopharmaceuticals developed Recombinant subunit vaccine based on the trimeric S protein (S-Trimer) of the COVID-19 coronavirus, which is responsible for binding with the host cell and causing a viral infection. This vaccine is in phase I clinical trial to evaluate the safety and the immunogenicity of the S-Trimer with AS03 and CpG1018 plus Alum adjuvants [20]. This vaccine will be subjected to clinical trial soon. Also, Tonix Pharmaceuticals designed TNX-1800 to express the spike protein, derived from the virus that causes the SARS-CoV-2 infection and this vaccine at the low dose of one 106 PFU is a perfect dose for a one shot vaccine in humans. Sputnik V (Gam-COVID-Vac) is an adenoviral-based, two part vaccine against the SARS-CoV-2 coronavirus produced in HEK293 cell lines. It reduces the time taken for the actual development of immunity to SARS-CoV-2 infection [21]. Covishield otherwise named as Vaxzevria, produced by Oxford-AstraZeneca jab in India works in a similar way as Sputnik V. It is prescribed to be administered in two doses between twelve to sixteen weeks apart [12]. A modified coronavirus vaccine, Infectious Bronchitis Virus (IBV) vaccine has been developed to treat poultry coronavirus, which has high genetic similarity to the human coronavirus [22]. The vaccine has demonstrated efficacy in preclinical trials conducted by the Volcani Institute. Yet another adjuvant vaccine, BPI-002 developed by beyond spring is a small molecule agent that is indicated for treating various infections including COVID-19. The cocktail of BPI-002 with another COVID-19 vaccine is assumed to generate long term protection against viral infections. Likewise, there are numerous other vaccines which are under developmental stage, either in in-vivo testing or in clinical trials [Table/Fig-4] [22-36].

4. Inactivated Vaccines

Covaxin (BBV152) is the India's first indigenous vaccine against COVID-19 infection, developed by Bharat Biotech in collaboration

Name of the vaccine	Stage of development	Type of vaccine	Mode of action	Name of the company
Kevzara [13]	Phase I/III clinical trial	Fully human monoclonal antibody	It is approved for the treatment of rheumatoid arthritis and it is known to block the IL-6 pathway, which causes an overactive inflammatory response in the lungs of COVID-19 patients.	Regeneron pharmaceuticals, Inc. New York.
REGN3048-3051 [14]	Human clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID)	Passive vaccine	It is the combination of neutralising monoclonal antibodies REGN3048 and REGN3051	Regeneron pharmaceuticals, Inc. New York.
AdCOVID [15]	Immunogenicity studies	Single dose intranasal vaccine	It is used against Influenza for humans and vaccine for inhalation	Altimmune, University of Alabama at Birmingham (UAB).
TZLS-501 [16]	Phase I study is anticipated to be complete in Q1 2021	Monoclonal antibody	It is a human anti-IL-6 Receptor (IL-6R). The drug works by binding to IL-6R and depleting the amount of IL-6 circulating in the body thereby reducing chronic lung inflammation.	Tiziana Life Sciences plc. London, UK.
TJM2 [17]	The company will commence development after receiving approval for the Investigational New Drug (IND) application from the U.S. Food and Drug Administration (FDA).	Neutralising antibody	The human Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), which is responsible for acute and chronic inflammation.	I-Mab Biopharma Co., Ltd., China.
Gimsilumab [18]	Phase II	Human monoclonal antibody	The drug targets GM-CSF, and is expected to reduce lung damage and reduce mortality rate in COVID-19 patients.	Roivant Sciences Ltd., Basel, Switzerland.
EpiVac Corona [19]	Approved vaccine	Chemically synthesised Peptide vaccine conjugated to a carrier protein	Antigens based vaccine that provokes an immune reaction against COVID-19	Vektor State Research Center of Virology and Biotechnology, Russia.

[Table/Fig-3]: Antibody-based vaccines for COVID-19 [13-19].

Name of the vaccine	Stage of development	Type of vaccine	Mode of action	Name of the company
Infectious bronchitis virus (IBV) vaccine [22]	Completed preclinical studies	Live attenuated IBV vaccines	It is developed for avian coronavirus and modified to treat COVID-19. IBV has high genetic similarity with human coronavirus.	Volcani Institute, MIGAL Research Institute, Israel
Potential COVID-19 vaccine [23]	Preclinical evaluation	Microneedle array with fingertip-sized patch of 400 tiny needles with spike protein.	The protein pieces are manufactured by a "cell factory", which is layered upon cultured cells engineered to express the SARS-CoV-2 spike protein that can induce the immune response.	University of Pittsburgh School of Medicine
VPM1002 [24]	Implementation of Phase III study	Bacillus Calmette-Guérin (BCG) vaccine	It can protect not only against tuberculosis but also against viral infections of the respiratory tract	Max Planck Institute for Infection Biology, Germany
AT-100 (rhSP-D) [25]	Completed Preclinical study	Novel human recombinant protein	It is a recombinant form of human surfactant protein-D (rhSP-D) and a normal protein component of lung surfactant that performs three critical roles in maintaining healthy lung function, anti-inflammatory, Immunomodulatory and surfactant homeostasis.	Airway Therapeutics, Inc. Ohio
Recombinant subunit S-Trimer vaccine [26]	Phase I clinical trial	Recombinant subunit vaccine	It is developed based on the trimeric S-protein (S-Trimer) of the COVID-19 coronavirus	Clover Biopharmaceuticals, Inc. China
BPI-002 [27]	Filled US patent	Cocktail of BPI-002 with other COVID vaccine	It is a small molecule agent that can activate CD4+ helper T cells and CD8+ cytotoxic T cells and generating an immune response in the body	Beyond Spring Inc. USA
Oral recombinant vaccine [28]	Preclinical stage	Recombinant vaccine	Oral H1 influenza tablet vaccine primarily protected against infection based on mucosal immunity	Vaxart, Inc. USA
Tnx1800 [29]	Preclinical stage with Phase I human trial to be commenced in the second half of 2021	Recombinant vaccine	It is designed to express the Spike protein from the SARS-CoV-2 virus that causes COVID-19	Tonix pharmaceuticals, Inc. New York
NVX-COV-2373 [30]	Scale-up for preliminary clinical trials.	Recombinant protein nanoparticle vaccine	The vaccine is designed to primarily bind to the major surface S-protein of coronavirus	Novavax, Inc., USA.
Sputnik V [31]	Approved vaccine	Recombinant adenovirus vaccine (rAd26 and rAd5)	It uses a weakened virus to deliver small parts of a pathogen and stimulate the immune response	Gamaleya Research Institute, Acellena Contract Drug Research and Development, Russia
AstraZeneca (AZD1222); also known as Vaxzevria and Covishield [32]	Approved vaccine	Adenovirus vaccine	It is based on the virus's genetic instructions for building the spike protein	Oxford University and AstraZeneca, UK
Janssen (JNJ-78436735; Ad26.COV2.S) [33]	Approved vaccine	Non replicating viral vector	Recombinant vaccine candidate that contains an adenovirus serotype 26 (Ad26) vector expressing a stabilised SARS-CoV-2 spike protein	Johnson and Johnson (J&J), New Jersey, USA; Janssen Pharmaceutical, Beerse, Belgium; and the Beth Israel Deaconess Medical Center, Boston, USA
Vaxart oral COVID-19 (VXA-CoV2-1) [34]	Phase I Clinical trials	Recombinant vaccine (adenovirus type 5 vector)	VXA-CoV2-1 targets both the spike protein (S) and nucleoprotein (N) and triggers mucosal immune responses in humans	Vaxart, California, USA

Nanocovax [35]	Phase III Clinical trials	Recombinant vaccine (Spike protein)	It is a protein subunit vaccine developed using recombinant S-protein subunit binding to silica nanoparticles. S-protein was produced by using recombinant DNA technology on CHO cells (Chinese hamster ovary cells)	Nanogen Biopharmaceutical, Vietnam
IIBR-100 (BriLife) [36]	Phase I/II Clinical trials	Recombinant Vesicular Stomatitis Virus (rVSV) vaccine	Brilife is a vector based vaccine that takes VSV and genetically engineers it to express the spike protein of the SARS-CoV-2 beta coronavirus on its envelope. The human body recognises the spike protein expressed on the envelope and begins to develop an immunological response.	Israel Institute for Biological Research, Ness Ziona, Israel; Hadassah Medical Center, Jerusalem, Israel; Sheba Medical Center Hospital, Israel.

[Table/Fig-4]: Recombinant vaccines for COVID-19 [22-36].

with the Indian Council of Medical Research (ICMR) and National Institute of Virology. Being an inactivated vaccine, the pathogen's ability to replicate will be reduced maintaining the cellular integrity intact, which could be recognised by the immune system and produce the antibodies. It has the ability to target even the mutated strains from UK. It has been approved to use in two dose regimen at four weeks interval [37]. It was developed from NIV-2020-770 and a Vero cell platform (CCL-81) with adjuncts of either aluminum hydroxide gel (Algel) or a novel TLR7/8 agonist adsorbed gel. Other inactivated vaccines such as BBIBP-CorV [38], CoronaVac or Sinovac [39], WIBP-CorV [40], CoviVac [41], QazVac [42] are still in phase III clinical trials [Table/Fig-5] [38-43].

REPURPOSING OF DRUGS AGAINST COVID-19

Currently, allopathic medicines are being repurposed in various countries to battle COVID-19 infection, since it has entered the stage beyond containment. Repurposing drugs is an emergency contingency strategy which was already being tested and found to be safe for humans and so, does not require a clinical trial period. Retasking the drugs that are intended for other diseases may or may not bring complete clinical cure for the COVID infection, hence combinatorial or cocktail of drugs could be considered effective for the present scenario.

Specifically, HIV protease inhibitors that functions as an antiviral drug like Darunavir, Nelfinavir, Saquinavir, lopinavir/ritonavir (Kaletra) [44] are under investigation against COVID-19 infection. Combination of Kaletra with Arbidol, a drug that prevents the virus from attaching to the host is also been tested against COVID-19 infection. Another combination of Kaletra with anti-influenza drug, Oseltamivir (Tamiflu) showed promising effect within 48 hours of treatment in COVID-19 patients.

Notably, Remdesivir [45], an adenosine analog interferes with the copying machinery of viral RNA polymerase produces premature termination of viral RNA. It is used for treating Ebola virus disease and Marburg virus infections and found to be more effective against Middle East Respiratory Syndrome (MERS). The antimalarial drug and broad spectrum antiviral drug, chloroquine and its derivative, hydroxychloroquine, is currently redirected as a promising drug for treating coronavirus. It is found to change the pH level of the endosome, interferes with the glycosylation of cellular receptor of coronavirus, thus preventing the endosome from releasing the virus into cytoplasm. Remdesivir and chloroquine combination are highly effective in the control of COVID-19 infection, in vitro [46].

Japanese flu drug named Favipiravir [47], selectively inhibits viral RNA-dependent RNA polymerase and has been found to be effective with the patients with mild to moderate symptoms. However, Japanese health ministry suggested the drug as ineffective against patients with severe lung infection. A similar effect was also observed when the patients treated with the cocktail of the HIV antiretroviral drugs, lopinavir and ritonavir. In addition, APN01 [48], ACE2 protein decoy, which was designed to treat SARS, is now being redirected to decoy the SARS-CoV-2 from entering the cells. Although the drug crossed the phase I and phase II clinical trials, a few reports reveal that the drug does not protect people with ARDS. As discussed, various combinations of drugs seem to be more promising in reducing the symptoms of COVID-19 infection [Table/Fig-6] [49-63].

Name of the vaccine	Stage of development	Type of vaccine	Mode of action	Name of the company
BBIBP-CorV [38]	Phase III Clinical trial	Inactivated vaccine	Cultured virus on Vero cells soaked in beta-propiolactone with an aluminium based adjuvant used to activate the immune response	Beijing Institute of Biological Products, China; National Pharmaceutical Group (Sinopharm), China.
CoronaVac or Sinovac [39]	Phase III Clinical trial	Inactivated vaccine (formalin with alum adjuvant)	Cultured virus on Vero cells soaked in beta-propiolactone with an aluminium based adjuvant used to activate the immune response	Sinovac, China
WIBP-CorV [40]	Phase III Clinical trial	Inactivated vaccine	Chemically inactivated whole virus vaccines for COVID-19.	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm), China
CoviVac [41]	Phase III Clinical trial	Inactivated vaccine	Inactivated virus based vaccine for COVID-19	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products, Russia
QazVac (QazCovid-in) [42]	Phase III Clinical trial	Inactivated vaccine	Inactivated virus based vaccine for COVID-19	Research Institute for Biological Safety Problems, Kazakhstan
Covaxin (BBV152) [43]	Approved	Inactivated vaccine	The vaccine is derived from the Vero cell platform	Bharat Biotech, ICMR; Ocugen, India.

[Table/Fig-5]: Inactivated vaccines for COVID-19 [38-43].

Drug name	Actual intention	Developmental stage	Mode of action	Company
Hydroxychloroquine [49]	Antimalarial drug	Clinical trial for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection	It is effective in inhibiting SARS-CoV-2 infection in vitro	Ipca Laboratories, Zydus Cadila and Wallace Pharmaceuticals Ltd., India.
Actemra [49]	Immunosuppressive drug	Clinical train in China, Italy, Switzerland, Spain, USA	Disease Modifying Antirheumatic Drugs (DMARDs) that can prevent cytokine storms or overreaction of the immune system	Roche Holding AG, Switzerland.
Galidesivir (BCX4430) [49]	Drug against Ebola, Zika, Marburg, and Yellow fever	Advanced development stage under the Animal Rule Clinical Trail Phase I, Brazil	It is a nucleoside RNA polymerase inhibitor that disrupts the process of viral replication	Biocryst Pharmaceutical Inc., USA.
AmnioBoost [49]	Osteoarthritis drug	Phase I clinical trial in Seattle	It reduces the production of proinflammatory cytokines	Lattice Biologics, Ltd., USA.

Sarilumab [49]	Drug for rheumatoid arthritis-Anti-IL6	Clinical trial against COVID-19.	DMARDs against the IL-6 receptor, a human antibody that may prevent the activity of IL-6 for the treatment of COVID-19	Regeneron and Sanofi Inc. New York.
Losartan [49]	AT1R blockers	Clinical trial against COVID-19 in USA	Angiotensin II receptor antagonist that blocks the binding of angiotensin II to the angiotensin I (AT1) receptor.	Sandoz Inc. USA.
Remdesivir (GS-5734) [50]	Drug for Ebola virus disease and Marburg virus infections	Two phase III randomised clinical trials	Antiviral drug in the class of nucleotide analogs, that interferes with the action of viral RNA polymerase	Gilead Sciences, Inc.
Darunavir [51]	Protease Inhibitor in HIV infection	In vitro evaluation	It acts on the HIV aspartyl protease by which the virus cleaves the HIV polyprotein into its functional fragments	Janssen, Pharmaceutical companies, Belgium.
Nelfinavir [52]	Antiretroviral protease inhibitor	In vitro study and virtual screening	It inhibits HIV-1 and HIV-2 proteases	Agouron Pharmaceutical Inc., USA.
Saquinavir [53]	Protease inhibitor	In-silico analysis	Antiretroviral drug that inhibits HIV-1 and HIV-2 proteases	Roche Holding AG, Switzerland.
lopinavir/ritonavir (Kaletra or Aluvia) [54]	HIV Protease Inhibitor	Clinical trial in China	Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the Non Human Primates (NHP) model of the MERS. Ritonavir is a peptidomimetic agent that inhibits both HIV-1 and HIV-2 proteases	Abbvie Inc. USA.
Moexipril [55]	Drug for Hypertension and congestive heart failure	Suggested drug for COVID-19	It is a non-sulfhydryl Angiotensin Converting Enzyme (ACE) inhibitor which blocks the conversion of angiotensin I to angiotensin II	Schwarz Pharma, Inc. USA.
Daunorubicin [56]	Anticancer chemotherapy drug	Suggested drug for COVID-19 and in-silico screening	Anti-tumour antibiotic that blocks an enzyme called topoisomerase 2	Gilead sciences Inc., USA.
Mitoxantrone [57]	Antineoplastic antibiotic	Suggested for COVID-19 and in-silico screening	It is used to treat acute leukaemia, lymphoma, and prostate and breast cancer, severe multiple sclerosis. It intercalates and crosslinks DNA, thereby disrupting DNA and RNA replication	Pfizer Inc., USA.
Bepotastine [58]	Antihistamine for allergic rhinitis	suggested drug for COVID-19	Antihistamine that inhibits the release of histamine from mast cells.	Tanabe Seiyaku Co., Ltd.
Atovaquone [59]	Antimalarial drug	Suggested for COVID-19 and in-silico screening, Clinical trial-Not yet recruiting	Antimalarial and Antipneumocystis that blocks the mitochondrial electron transport at complex III of the respiratory chain of protozoa	GlaxoSmithKline plc. UK.
Favipiravir [60]	Antiviral	Clinical trial in China, Italy	Antiviral drug that selectively inhibits viral RNA-dependent RNA polymerase	Toyama Chemical Co., Ltd. Japan.
Teicoplanin [61]	Antibiotic	Alternative drug for COVID-19	Antibiotic used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus and Enterococcus faecalis by targeting targets peptidoglycan synthesis	Sanofi-Aventis, Cipla (India).
OYA1 [62]	Broad spectrum antiviral drug	FDA approved drug for cancer	Antiviral drug against coronaviruses SARS-CoV-2 and MERS-CoV and also a dual target-specific antiviral against filoviruses such as Ebola virus.	OyaGen Inc., USA.
APN01 [63]	Clinical trial	Recombinant human ACE2	It mimics ACE2, acting as a decoy that binds to the virus and inactive. It reduces harmful inflammatory reactions in the lungs that occur in some patients with COVID-19	Apeiron Biologics Ag, Austria.

[Table/Fig-6]: Repurposed drugs against COVID-19 [49-63].

Challenges Encountered in Vaccine Development and Drug Repurposing

The major concern with respect to vaccine development is the timely response to the pandemic or epidemic situation. However, the effective development of vaccine is merely dependent on the coordination of policy makers, researchers, funding agencies, manufacturers and regulators. Time to complete the pre-clinical testing in cell culture systems, animal models and in humans, financial support, postlicensure monitoring of vaccine, is quite challenging in the vaccine development. The development of vaccine put forth various challenges such as its ability to target the specific variants of SARS-CoV-2, its efficacy against mutant strains, and its ability to provide herd immunity to the population.

Considering all these factors in a pandemic outbreak like SARS-CoV-2, the overall time and money taken to complete the process of production of vaccine till the approval by Food and Drug Administration (FDA) will take a minimum of 1 to 1.6 years, charging loss of huge human lives. Despite the advances in using the de-risked compounds for SARS-CoV-2, there are numerous technological and regulatory challenges that need to be addressed for the approval. Repurposed drugs do not always succeed and mostly they fail to pass the phase III trial. Barriers at patent considerations, regulatory and organisational restrictions must be encountered. Legal and intellectual property barriers also need to be addressed. The time and the efforts taken to overcome all these hurdles during an epidemic disaster delays the drug discovery.

Although, vaccine development and drug repurposing are considered as a promising area in drug discovery and therapeutics, value added herbal medicine is recommended as an immediate source of alternative medicine for viral diseases like SARS-CoV-2. Potential herbal medicines that are ethnically practiced as an antiviral drug could be possibly used to treat the different stages of COVID-19 infection, which will be discussed in the following section.

ALTERNATIVE BIOMEDICINE FOR CORONAVIRUS

During COVID-19 infection, the immune system provides defense just like it does to any other infectious organisms and other foreign invaders. But, the coronavirus virus employs different evasion mechanisms to escape the host immune system [64]. The strategies of immune evasion are directed towards humoral, cell-mediated and effector mechanisms. It is also noted that immune

pathogenesis is associated with uncontrolled immune response leading to pulmonary tissue damage, functional impairment, and reduced lung capacity. Immune insufficiency or misdirection may increase viral replication and cause tissue damages [65]. Thus, an effective alternative medicine is vital to curb the viral multiplication and prevent the disease. Application of the traditional medicine along with modern medicine might boost the immune system to fight against the deadliest coronavirus.

Despite the advancement in the vaccine or drug development, many viruses escape the conventional therapies due to the generation of viral mutants with enhanced virulence. Re-emerging viruses or virus variants like SARS-CoV-2 remains a threat to public health especially when there is no efficient vaccination or antiviral therapies. It is observed that only a few antiviral drugs approved by FDA are repurposed against COVID-19 infection, and limited vaccines are in clinical trials. The usage of specific viral enzyme specific inhibitors lead to the development of multidrug resistant mutants of SARS-CoV-2 [66]. Hence, there is an urge to identify an alternative strategy for the control of COVID-19 infection especially, when standard vaccines or therapies are still under clinical trials. Herbal medicines are the richest source of novel antiviral compounds and many countries especially in Asia prefer traditional medicines than the conventional medicines or the combination of both [67]. Here, we have systematically reviewed several herbal plants; these plants with antiviral property can be gainfully used in the management of COVID-19 infections such as fever, pneumonia, cold and cough, asthma and bronchitis, kidney dysfunction.

Antiviral and Antibacterial Activity of Traditional Medicine, Aegle Marmelos

Commonly called as 'Vilvam' in vernacular Tamil, it has been widely used in indigenous systems of Indian medicine. It possesses antiviral activity against human coxsackie viruses B1-B6. It appears to inhibit the viral replication with the least host cytotoxicity than the modern viricidal drug ribavirin, that usually acts in later stage of viral replication [68]. Shorea robusta, one of the most important traditional Indian medicinal plant, also named as 'Venkungiliyam' is found to exhibit antiinflammatory, antipyretic activity [69] and antiviral activity against herpes simplex virus [70]. Earlier, Nilavembu kudineer (NVK) has been used to cure the epidemic outbreak caused by Dengue, by Flavivirus (DENV) and Chikungunya by an alphavirus, (CHIKV) [71]. As per Siddha medicine, the regimen of medication of NVK (otherwise called as neem of ground) is used as an antiviral concoction. It is a polyherbal concoction with Andrographis paniculata as the chief ingredient that controls fever in a comprehensive manner through its healing effects of temperature regulation, inflammation control and body pain relief and thus boost the immunity [72]. Allium sativum, commonly called as 'Garlic' is widely used as a spice in Cameroon and has been found to have antimalarial activity [73]. Indian folklore of Achyranthes aspera (Nayurivi) is used in treatment of cough, bronchitis and rheumatism, malarial fever, dysentery, and asthma [74].

Alternative Medicine for Respiratory Diseases and Fever

Albizia lebbeck, otherwise called as 'Vagai', is highly recommended in Ayurvedic system for bronchial asthma [75]. Stem bark decoction has been found to decrease the histamine induced bronchospasm, thus, protective against bronchial asthma [76]. Another important folk medicine, Justicia Adathoda, popularly called as 'Adathodaiillai' is widely used for the treatment of respiratory diseases as well as inflammation like arthritis and rheumatism [77]. Two glycoside compounds from yet another species, Justicia reptans displays a clear viricidal effect on HIV [78]. 'Catechu', extract from Acacia catechu effectively been used for treating fever and the presence of tannins and polyphenols imparts astringent activity for curing throat infection [79]. Similarly, Coleus aromaticus is traditionally used in medicinal system especially for severe bronchitis, asthma, fever, common cold and cough [80]. Ethno medical use of Plectranthus amboinicus or 'Karpuravalli', has been found to treat common cold [81].

Combinations of Traditional Plants against COVID-19 Infection

Combination of traditional medicine on top of the standard modern medicine is found to be a life supportive system preventing the symptoms of COVID-19 infection. Earlier, SARS clinical data in China have shown that about 40-60% of the infected individuals have received Chinese traditional medicine along with the modern medicine, that helped in decreasing the mortality rate [82]. Similarly, Ministry of Ayurveda, Yoga and Naturopathy Unani, Siddha, Sowa-Rigpa and Homeopathy (AYUSH), Government of India with the recommendations (D.O.No.S 16030/18/2019-NAM; dated 06th March, 2020) from the Research council has announced a combinatorial formulation of 15 different plant sources in the name of "Kabasura Kudineer" for symptom management of COVID-19 like illness [83]. It makes the body resistant against the viral infection, and also found to be effective against the treatment of swine flu. The decoction includes the combination of the following plants [84], Nilavembu (Andrographis paniculata), Kanduparangi (Clerodendrum serratum), Chukku (Zingiber Officinale), Thippili (Piper longum), lavangam (Syzygium aromaticum), Adathodaiver (root of Justicia beddomei), Cirukancori Ver (Tragia involucrate), Seenthil (Tinosporia cordifolia), Karpooravalli (Anisochilus carnosus), Koraikizhangu (Cyperus rotundus), Kostam (Costus speciosus), Akkara (Anacyclus pyrethrum), Vattathiruppi Ver (Sida acuta), Mulli Ver (Hygrophilla auriculata) and Kadukkaithol (Terminalia chebula). Apart from the above mentioned formulation, there are other plant sources and formulations available [85], which might be in practice specific to each region/ country. In the present pandemic outbreak caused by SARS-CoV-2, the only immediate alternative that we can look as a preventive measure rather than treating the disease, could be the use of plant based medicines.

CONCLUSION(S)

Intense knowledge on the pathogenic characteristics, immune response and epidemiology of SARS-CoV-2 virus is needed to combat the challenges faced in strain specific drug discovery. Although many Research and Development (R and D) companies in collaboration with academic institutes are striving to develop vaccine and drugs against this pandemic disease, an approximate period of 1 to 2 years is essential to complete the clinical trial and secure the FDA approval before it reaches the common man. The challenges encountered in the vaccine and drug development allow us to look for the better solution with an alternative medicine. Various plant sources of Asian origin, which could be possibly used for the symptoms of COVID-19 infection, are described in this review. Likewise, country specific ethnic usage of plant sources might be therapeutically investigated to find out the optimal mix with the modern medicine, that could either help in increasing the immunity against the virus or control the symptoms of COVID infection.

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