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Therapeutic opportunities to manage COVID-19/SARS-CoV-2 infection: Present and future

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A severe form of respiratory disease – COVID-19, caused by SARS-CoV-2 infection, has evolved into a pandemic resulting in significant morbidity and mortality. The unabated spread of the disease is due to lack of vaccine and effective therapeutic agents against this novel virus. Hence, the situation demands an immediate need to explore all the plausible therapeutic and prophylactic strategies that can be made available to stem the spread of the disease. Towards this effort, the current review outlines the key aspects of the pathobiology associated with the morbidity and mortality in COVID-19 patients, which includes a viral response phase and an exaggerated host response phase. The review also summarizes therapeutic agents that are currently being explored along with those with potential for consideration. The broad groups of therapeutic agents discussed include those that: (i) block viral entry to host cells, (ii) block viral replication and survival in host cells, and (iii) dampen exaggerated host immune response. The various kinds of pharmaceutical prophylactic options that may be followed to prevent COVID-19 have also been discussed.

Key words: COVID-19, prophylaxis, SARS-CoV-2, therapy

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection associated respiratory disease – COVID-19 (2019-nCoV) evolved into a pandemic in about three months, from a cluster of pneumonia cases in China in mid-December 2019 to 267,013 cases in 184 countries with a mortality rate of 4.2% (11,201) as on March 22nd 2020. The situation clearly indicates the urgent and immediate need to explore all the therapeutic and prophylactic strategies that can be made available to stem the spread of the disease. Briefly, SARS-CoV-2 (family Coronaviridae; genus Betacoronavirus; subgenus Sarbecovirus) is an enveloped virus with a positive sense single-stranded RNA genome. It is suspected to have been transmitted from bats or through unknown intermediates to humans. Effective human-to-human transmission even by asymptomatic and/or pre-symptomatic carriers has been a major reason underlying the rapid worldwide spread of the disease. It is known to be transmissible via direct contact, respiratory secretions and droplets, and could remain stable on surfaces for days. The presence of the virus in faecal swab, blood and tears or conjunctival secretions indicates that other modes of transmission are also plausible. High morbidity have been observed among the elderly, those with additional co-morbidities and those under immunosuppression. Though the incubation period was reported to between 1 to 14 days, it has been found to be contagious even during the latency period.

Current confirmatory diagnosis for SARS-CoV-2 infection is by the detection of its genome by real-time PCR in samples collected from nasal, throat swabs and/or blood. The results are sometimes validated by next-generation sequencing. Very recently, serological assays to determine the presence of virus by measuring antibody titres and seroconversion of SARS-CoV-2 have been developed and proposed for use. The potential of such tests would be manifold, from prognosticating, identifying suitable convalescent serum and redeployment of health care personnel based on sero status. Another important aspect in risk stratification can also be based on HLA (Human Leukocyte Antigen) types, as earlier reports have shown association between specific HLA types and susceptibility to SARS-CoV and MERS-CoV disease. Laboratory findings in COVID-19 shows lymphocytopenia, but high numbers of neutrophils, increased blood urea, creatinine and inflammatory factors were also observed.

Mechanisms underlying COVID-19 associated morbidity and mortality

SARS-CoV-2 causes COVID-19, which manifests as flu-like illness with fever, cough, sore throat, fatigue, dyspnoea, occasional diarrhoea and vomiting. In a select group of patients such as the elderly and immunocompromised individuals, the condition deteriorates to acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure resulting in mortality.

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As shown in Fig. 1, earlier and milder symptoms are due to viral infection and proportionate immune response to it (viral response phase). This phase can be managed by pharmaceutical agents directed against the various aspects of the viral life cycle. Most often, the grave morbidity and mortality associated with SAR-CoV-2 infection is due to the collateral damage caused by exaggerated and unabated immune response mounted by the host to protect against the infection (exaggerated host response phase). This stage would require profound immune dampening along with anti-viral strategies.

The milder symptoms that present during the viral response phase is due to the action of virus invading the respiratory mucosa and infecting the cells, which is sensed by the immune system that mounts a proportionate response against it. The envelope spike glycoprotein (S) protein of SARS-CoV-2 binds to its host cellular receptor Angiotensin-converting enzyme 2 (ACE2) on the cell surface to gain entry via both clathrin-dependent and -independent endocytosis. The S protein then needs to be cleaved by cellular protease (serine protease, TMPRSS2), termed S protein priming, such that the viral and host cell membranes can fuse. After the nucleoprotein genome is released into the cytoplasm, the viral RNA directs a program of viral protein production and genome synthesis that results in subsequent viral replication and final release of virus from the cell. However, the presence of viral RNA genome triggers an anti-viral response through the activation of pattern recognition receptors such as toll-like receptors (TLR) -3, -7, -8 and 9. This protective response includes the induction of type 1 interferons and pro-inflammatory cytokines directed to stop viral propagation in the host cells. Furthermore, presentation of the viral antigen by the infected cells also renders cellular and humoral immunity, in the form of virus-specific T cells and virus-specific antibody. Pharmaceutical strategies that includes the blockade of viral entry to host cells and, blockade of viral replication and release would be effective in this phase to alleviate symptoms, reduce transmission and deterioration of the condition.

ARDS has been reported as the major cause of death among COVID-19 patients and was the case with SARS-CoV and MERS-CoV infections. Cytokine release syndrome (CRS), is characterized by large scale production and release of pro-inflammatory cytokines and chemokines due to hyper activation of the immune system causing damage to tissues and multi-organ failure. This stage comprises of widespread injury to the vascular endothelium by the circulating inflammatory cytokines such as IL-6, IL-1 etc., followed by enhanced expression and presence of these inflammatory factors in the interstitial space resulting in injury to the tissue parenchyma. More recently, a report illustrated the absence of wound-healing macrophages, faster neutralizing antibody responses along with increased pro-inflammatory factors in patients who succumbed to SARS-CoV. The immediate effort during ARDS is normally focussed on dampening the exaggerated immune response to prevent further damage to the tissues. A more effective approach is to prevent the progression of the disease by close monitoring and evidence based use of prophylactic immune modulation along with anti-viral agents.

Immunophenotyping efforts have indicated systemic and tissue specific immune profile in COVID-19 patients. Along with the levels of inflammatory factors, the proportion of immune cells, its subsets, its activation status, its response and kinetics have been associated with disease state and prognosis. Such information could be used to prognosticate or modulate specific immune cell subtypes to improve anti-viral immunity. However, as more data is reported on the disease progression and outcomes of therapy, a more consolidated profile will emerge with reference the status of immune cell and their role in COVID-19 pathobiology and disease resolution.

Strategies to mitigate COVID-19 associated morbidity and mortality

This section enumerates the various therapeutic agents along with their mechanism of action to target various aspects of the viral life cycle and exaggerated host immune response. The current and possible therapeutic strategies for the management of COVID-19/SARS-CoV-2 infection are summarized in Fig. 2 and Table 1.

Prevention of virus entry into host cells

Prevention of attachment

Since SARS-CoV-2 utilises the host cell surface receptor ACE2 to attach itself via its Spike protein (S) and gain entry, it is an attractive target for preventing viral uptake. The options to block viral entry include the use of natural neutralizing antibodies from convalescent sera (discussed elsewhere in the manuscript) and engineered antibodies. Engineered antibodies or neutralizing fragments can be in various formats, such as soluble receptor-binding domain (based on SAR-S protein) that would occupy ACE2 and prevent access to SARS-CoV-2; antibodies or single chain variable fragment that would bind to ACE2 and prevent access to SARS-CoV-2, and soluble version of ACE2, which will bind to SARS-CoV-2, thus competitively sequestering it away from cell surface bound ACE2 in host cells. The presence of Fc portion in natural and engineered antibodies or fragments would enable the elimination of the virus via phagocytosis and immune activation. It should be noted that due to the functional complexity that underlies renin angiotensin aldosterone system and the lack of robust information on the status of ACE2 expression in various tissue following the use of ACE inhibitors and angiotensin receptor blockers, it is difficult to speculate on the relevance of these ACE modulators in COVID-19. However, ACE inhibitors and angiotensin receptor blockers have been shown to decrease severe lung injury in certain virus mediated respiratory conditions. Emodin (a naturally occurring anthraquinone) and promazine (phenothiazine class of anti-psychotics) have been shown to interrupt the binding of S protein with ACE2. Further, drug-repurposing strategies have suggested possible small molecule drugs that may bind to S-protein to disrupt S protein-ACE2 interaction.

Prevention of fusion

The next critical stage in viral entry into the host cell is S protein priming, where the S protein needs to be cleaved by cellular proteases such as transmembrane protease serine 2 (TMPRSS2), furin and cathepsins for the viral and cellular membranes to fuse. Specifically, S protein priming by the serine protease TMPRSS2 is crucial for SARS-CoV infection of host target cells. Hence, targeting CoV entry by using protease inhibitors would be beneficial. TMPRSS2 is shown to be blocked by serine protease inhibitors such as camostat and nafamostat.
Figure 1: Types of morbidity based on underlying mechanisms in COVID-19 patients. The schema represents a continuum with an early viral response phase followed by an exaggerated host immune response phase, with each phase benefiting from a distinct therapeutic approach for its management.

Figure 2: Therapeutic strategies in the management of COVID-19/SARS-CoV-2 infection

Chloroquine, a 9-aminoquinoline is well-known for its effective use in the management and prevention of malaria. It evolved as an anti-viral agent by having more than one mechanism in inhibiting the viral life cycle. Firstly, as it is a weak base, it increases the pH of acidic vesicles such as endosomes and lysosomes, thereby preventing the viral envelope from uncoating and releasing the RNA into the host cell cytoplasm. It is also known that chloroquine impairs virus replication, assembly and release. Chloroquine was also reported to impair glycosylation of ACE2 which could possibly interrupt the interaction between S protein and ACE2. Interestingly, anti-viral effects of chloroquine were
### Table 1: Current and possible therapeutic strategies for the management of COVID-19/SARS-CoV-2 infection

| Therapeutic agents | Possible COVID-19 indication | Mechanism of action relevant to COVID-19 | Original indication of the agent | Dosage information relevant to COVID-19 |
|--------------------|-----------------------------|-----------------------------------------|---------------------------------|---------------------------------------|
| Hydroxychloroquine | Off-label use for anti-viral response | Alters endosomal pH in host cells, thus, preventing the viral envelope from uncoating and releasing the RNA into the host cell cytoplasm. It is also known to disrupt viral S protein interaction with ACE2 by impairment of glycosylation of ACE2, which would prevent the SARS-CoV-2 from entering host cells. In addition, it has immunomodulatory or anti-inflammatory effects as well. | Malaria, autoimmune conditions | Treatment: 400 mg BID x 1 day, then 200 mg BID x 5 days; 200 mg TID x 10 days. Prophylaxis: 400 mg BID x 1, then 400 mg once weekly for 7 weeks. Prophylaxis: 400 mg BID x 1, then 400 mg once weekly for 3 weeks. |
| Camostat           | Off-label use for anti-viral response | Serine protease inhibitor that inhibits TMPRSS2 associated fusion process which would prevent the SARS-CoV-2 from entering host cells | Chronic pancreatitis | TBP |
| Nafamostat         | Off-label use for anti-viral response | Serine protease inhibitor that inhibits TMPRSS2 associated fusion process which would prevent the SARS-CoV-2 from entering host cells | Acute pancreatitis, as an anticoagulant to prevent blood clot formation during extracorporeal circulation | TBP |
| Lopinavir-Ritonavir| Off-label use for anti-viral response | Viral protease inhibitor that prevents proteolytic cleavage of the viral polyprotein precursors into individual functional proteins | Human immunodeficiency virus infection | 400/100 mg 5 ml suspension BID (or) 200/50 mg 2 Tab BID. 400/100 mg BID x 14 days. 500 mg once, twice a day, 2 weeks. |
| Nelfinavir         | Off-label use for anti-viral response | Viral protease inhibitor that prevents proteolytic cleavage of the viral polyprotein precursors into individual functional proteins | Human immunodeficiency virus infection | TBP |
| Remdesivir         | Investigational drug for anti-viral response | Nucleotide analog that specifically inhibits RNA-dependent RNA polymerase and prevents viral replication | Ebola virus, MERS-CoV | Ongoing clinical trial (USA - NCT04280705; NCT04292730; NCT04292899; EU - 2020-000841-15). 200 mg i.v on Day 1, followed by a 100 mg once-daily maintenance dose for the duration of the hospitalization according to the trial design. |
| Ribavirin          | Off-label use for anti-viral response | Nucleotide analog that specifically inhibits RNA-dependent RNA polymerase and prevents viral replication | Hepatitis C virus infection | 2.4 g orally as a loading dose followed by 1.2 g orally every 12 h. Duration of treatment up to 10 days. |
| Sofosbuvir         | Off-label use for anti-viral response | Nucleotide analog that specifically inhibits RNA-dependent RNA polymerase and prevents viral replication | Hepatitis C virus infection | TBP |
| Oseltamivir        | Off-label use for anti-viral response | Neuraminidase enzyme inhibitor that would prevent the virus from entering the host cell and reduces viral shedding and infectivity | Influenza | 75 mg BID |
| Zanamivir          | Off-label use for anti-viral response | Neuraminidase enzyme inhibitor that would prevent the virus from entering the host cell and reduces viral shedding and infectivity | Influenza | TBP |

Contd...
observed in both pre- and post-infection conditions, opening up the possibility of its use as both prophylactic and therapeutic agent.\(^5\) It has been proven to be effective against SARS-CoV-2 infection in vitro, particularly, hydroxychloroquine was observed to be more effective than chloroquine.\(^{30-32}\) More importantly, the chloroquine (chloroquine phosphate or hydroxychloroquine) was also observed to beneficial in the management of COVID-19 patients by reducing deterioration of disease and virus load.\(^{33,34}\) It is considered that chloroquine’s anti-viral and anti-inflammatory activities

| Therapeutic agents | Possible COVID-19 indication | Mechanism of action relevant to COVID-19 | Original indication of the agent | Dosage information relevant to COVID-19\(^6\) |
|--------------------|-----------------------------|----------------------------------------|---------------------------------|-----------------------------|
| Azithromycin       | As an antibiotic            | Prevents secondary bacterial infection. It has been reported to have anti-viral activity | Bacterial infections          | 500 mg x 1 day followed by 250 mg per day, x 4 days\(^{24}\) |
| Interferon alpha   | Off-label use to bring about anti-viral response | Induces the body’s innate anti-viral response | Viral infections and cancer | Pegylated interferon alfa-2a: 180 mg subcutaneously per week for 2 weeks. Pegylated interferon alfa 2b: 1.5 mcg/kg subcutaneously once per week x 2\(^2\) |
| Interferon beta    | Off-label use to bring about anti-viral response and immune modulation | Anti-viral and immunomodulatory effects | Multiple Sclerosis          | rIFN-b1a: 44 mg subcutaneously three times weekly\(^6\) |
| Convalescent sera  | Use for anti-viral response | Antibodies in the plasma/sera from convalescent patients might suppress viremia. | Prevention of infection | Useful when started at early stage of disease. Dose as per national or institutional guidelines |
| Emodin             | Investigational drug for anti-viral response | Disrupts the binding of viral S protein with ACE2 which would prevent the SARS-CoV-2 from entering host cells | Investigated for use in polycystic kidney disease | TBP |
| Promazine          | Off-label use for anti-viral response | Disrupts the binding of viral S protein with ACE2 which would prevent the SARS-CoV-2 from entering host cells | Psychomotor conditions (discontinued) | TBP |
| Corticosteroids    | Dampen exaggerated immune response | pan-immune suppression | Variety of inflammatory and autoimmune conditions | Methylprednisolone 40 mg q12h for 5 days\(^6\) |
| Tocilizumab        | Off-label use to dampen exaggerated immune response | Monoclonal antibody binds specifically to both soluble and membrane-bound IL-6 receptors to block IL-6-mediated responses | Rheumatoid arthritis | Dose as per national or institutional guidelines |
| Anakinra           | Off-label use to dampen exaggerated immune response | Interleukin 1 receptor antagonist protein prevent the effect of IL-1 by binding competitively to the Interleukin-1 type I receptor | Rheumatoid arthritis | Dose as per national or institutional guidelines |
| Ruxolitinib;       | Off-label use to dampen exaggerated immune response | Blocks cytokine mediated response by inhibiting the activation of Janus Associated Kinases (JAK) 1 and 2, a critical intracellular cytokine signalling event. | Myelofibrosis, autoimmune conditions | Dose as per national or institutional guidelines |
| Upadacitinib;      |                              |                                        |                                |                            |
| Baricitinib        |                              |                                        |                                |                            |
| IVIg               | Off-label use to dampen exaggerated immune response | Provides immunity against common pathogens and dampens immune activation by competitively blocking Fc gamma receptor mediated response | Immune deficiencies, and autoimmune conditions | Dose as per national or institutional guidelines |

\(^1\)COVID-19 management protocol, All India Institute of Medical Sciences, New Delhi, India. \(^2\)National Task Force for COVID-19, Indian Council of Medical Research, India (D.O.VIR/4/2020ECID-I). \(^3\)https://www.mohfw.gov.in/pdf/GuidelinesonClinicalManagementofCOVID1912020.pdf (Govt. of India). \(^4\)https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1. \(^5\) For asymptomatic health care workers involved in the care of suspected or confirmed cases of COVID-19. \(^6\)For asymptomatic household contacts of laboratory confirmed cases. \(^\text{Please refer to regulatory documents or black box warnings for potential side effects pertaining to the therapeutic agents. TBP-To be published}\)
could have contributed to the therapeutic effects observed in COVID-19 patients.\cite{53,55} Since, identification of the SARS-CoV-2 virus in tears or conjunctival secretions\cite{56} opened the possibility of additional modes of transmission, the use of chloroquine on the ocular surface\cite{56,57} can also be explored by studying the anti-viral effect using tolerable dose that can be used in eye drops.

**Prevention of viral replication and survival in host cells**

**Viral protease inhibitor**

Blocking key proteases such as coronavirus main protease (3CLpro) and papain-like protease (PLpro) are considered to be critical in blocking viral life cycle because they are necessary for the proteolysis of viral polyprotein into functional units.\cite{58} Hence, Lopinavir-Ritonavir protease inhibitors were explored in the management of COVID-19. Unfortunately, no therapeutic benefit was observed with Lopinavir-Ritonavir treatment beyond the standard care.\cite{59} However, this could be related to various factors such as the stage of the disease when it was administered, co-medications and adverse events that led to discontinuation of the regimen.\cite{60}

Cinanserin, flavonoids and diarylheptanoids have been reported to be inhibit 3CLpro or PLpro, hence, can be considered to be used to block SARS-CoV-2 replication.\cite{61,62} Another protease inhibitor, Nelfinavir, shown to inhibit SARS-CoV replication,\cite{63} also has the potential to block SAR-CoV-2 replication.

**Viral nucleic acid and protein synthesis inhibitors**

Remdesivir, a nucleoside analog that blocks the RNA-dependent RNA polymerase, is showing great promise in the management of COVID-19 patient.\cite{64} Interestingly, preclinical report suggests that the anti-viral activity of Remdesivir and type 1 interferon (IFN$\alpha$) was observed to be greater than Lopinavir–Ritonavir–IFN$\beta$ against MERS-CoV.\cite{65} Hence, a randomized, controlled clinical trial to evaluate the safety and efficacy of Remdesivir in COVID-19 has been initiated\cite{66} and outcome of similar trials in China is awaited. Ribavirin, which is also a nucleoside analog, is used to inhibit viral RNA synthesis and viral mRNA capping. Interestingly, ribavirin and IFN$\beta$ synergistically inhibited the replication of SARS-associated coronavirus in animal and human cell lines.\cite{67} Sofosbuvir, a nucleotide analog inhibitor, have been reported to exhibit potent anti-viral effects when used with ribavirin. More importantly, a report based on molecular docking showed tight binding of sofosbuvir and ribavirin to SARS-CoV-2 RNA-dependent RNA polymerase, thus suggesting its relevance in the management of COVID-19 patients.\cite{68} Type 1 interferons such IFN$\alpha$ and IFN$\beta$ are endogenous anti-viral proteins produced by the host cells in response to viral infection, which degrade viral RNA and block viral protein synthesis and assembly.\cite{69} Type 1 interferons have been available for clinical use for decades for the management of viral infection, tumours and auto-immune diseases.\cite{70}

The use of neuraminidase inhibitors such as oseltamivir and zanamivir have shown prevention of viral replication, budding and infectivity.\cite{71,72}

**Combination treatments**

Despite the favourable response observed with the use of Lopinavir-Ritonavir in the treatment of SARS,\cite{73} the more recent effort against SARS-CoV-2 did not turn out to be effective.\cite{74} Currently, Lopinavir-Ritonavir is being explored in combination with ribavirin and interferon-alpha\cite{75} or interferon beta for MERS-CoV.\cite{76} More recently, decrease in the viral load in COVID-19 patients by the use of hydroxychloroquine was observed to be enhanced in all the cases in the study arm when combined with azithromycin.\cite{77} This beneficial effect was observed to be particularly higher in cases with concomitant upper or lower respiratory tract infections compared to asymptomatic patients.\cite{78} Azithromycin was administered as a measure to prevent bacterial super-infection, it has been shown to have anti-viral effects as well.\cite{79,80} However, mechanism underlying the synergistic effect of hydroxychloroquine and azithromycin in decreasing the viral load is yet to be determined. Another combination of chloroquine with remdesivir was reported to be effective against SARS-CoV-2, albeit in vitro.\cite{81} These studies open up the rational use of potentially effective combinatorial treatment in future for the management of COVID-19.

**Active immunity**

It is evident that vaccination is the ideal strategy to provide long lasting immunity to a large proportion of the at risk population. Unfortunately, there isn’t any SAR-CoV-2 vaccine available at the moment. However, it is very encouraging that a total of 41 candidate vaccines are being developed against SAR-CoV-2 according to WHO’s draft landscape of COVID-19 candidate vaccines as of 13 March 2020.\cite{82} Different types of strategies such as DNA vaccine, RNA vaccine, live attenuated, formaldehyde inactivated, adenovirus-vector based, oral vaccine based, protein based and peptide based, are being employed against different components of SAR-CoV-2.

Currently, one of the candidates is in Phase 1 clinical trial,\cite{83} while the others are in various stages of preclinical development. The one in clinical trial, RNA-1273 is based on a RNA vaccine platform technology and is delivered via a novel lipid nanoparticle (LNP)-encapsulated mRNA against the stabilized spike protein.\cite{84}

**Passive immunity**

The principle underlying this strategy is to neutralize the virus from infecting the host cells using antibodies (also called as neutralizing antibodies, NAb) against them that can be administered safely to individuals in need.\cite{85} NABs can be obtained from the sera of patients from who have recovered from disease (convalescent sera) or can be engineered. Infected patients that recover completely, develop immunity against the virus that is likely mediated by either specific anti-viral antibodies or cell mediated immunity or both. This aspect has been harnessed by the use of convalescent sera/plasma therapy in the prevention and treatment of a variety of infections over decades, right from a century old Spanish flu to the more recent SARS and Ebola virus disease.\cite{86,87} World Health Organization (WHO) guidelines for the use of convalescent plasma in the management of Ebola virus disease\cite{88} can be adapted for immediate need in case of COVID-19. This provides instant immunity to susceptible or high-risk individuals and is typically more effective when used prophylactically or soon after the onset of early symptoms. The effectiveness of this strategy can be achieved by following identification of sera containing high titer of NABs and also by mitigating the risk associated with transfer of blood substances (such as other infections, serum sickness) or possible antibody-dependent enhancement of infection.\cite{89} Another aspect in providing passive immunity is by administering engineered neutralizing antibodies.\cite{90} This is being evaluated to combat MERS-CoV in phase 1 trials.\cite{91,92} Very recently, an engineered human monoclonal antibody
with the potential to block SARS-CoV-2 from infecting the cells has been developed.\[90] Though it was shown that the mAb binds to the spike receptor binding region, it did not compete with ACE2 binding and is thought to neutralize the virus in a receptor independent fashion.\[86] This approach emphasizes on engineering antibodies specific to the virus to prevent infection, reduce viral load or to be used in diagnostic systems.

Dampening hyper-immune activation and harnessing immune response

Corticosteroids, intravenous immunoglobulin (IVIg), monoclonal antibody based blockade of IL-6 (tocilizumab), interleukin 1 receptor antagonist protein (Anakinra) and JAK inhibition are the few strategies that have been proven to be effective in dampening exaggerated immune activation in a variety of diseases and treatment schedules.\[107,108] Hence, these will continue to be in the mainstream use in the management of cytokine release syndrome and associated pathologies in COVID-19 patients. In addition, to exaggerated response in later stages of the disease, dysregulated immune response was also observed in COVID-19 patients such as functionally exhausted cytotoxic T lymphocytes and natural killer cells due to increased expression of an inhibitory receptor, NKG2A that resulted in reduced anti-viral response.\[32] These receptors can be blocked using monoclonal antibodies to yield therapeutic benefits.\[90,92] Hence, such selective modulation of activatory and inhibitory receptors on anti-viral responsive lymphocytes at different stages would enable us to harness the immune response to drive infection control and disease resolution.

Potential role of natural products from Indian traditional medicine

Due to the rapid spread of the disease, it is of general interest to also consider alternative remedies. There have been descriptions of anti-viral treatments, even targeted to the coronavirus family in Chinese Traditional Medicine.\[92] Other natural products of Indian origin and Ayurvedic formulations have also been studied and used for their potential utility in various kinds of viral infections.\[93] However, it should be noted that none of such natural products are actually tested to treat COVID-19. Typically, the presence of a variety of phytochemicals such as flavonoids, tannins, triterpenes, phenolic acids, alkaloids, saponins, lignins, proteins and peptides provide a plethora of functions to such natural products and extracts which have been demonstrated to modulate various aspects of viral infection including virus entry, viral gene expression and replication.\[94] Although there is no direct evidence of the effect of such extracts, etc., on the SARS-CoV-2, common natural products such as curcumin and terpenoids can inhibit the CoV family member SARS\[95] while Withania somnifera (Ashwagandha) have been demonstrated to inhibit other RNA virus.\[79] Indeed several terpenoids and cannabinoids are being studied for their chemical action through docking studies on the viral protease are considered as possible prophylactic or therapeutic agents against SARS-CoV-2.\[95] Various natural products and their combinations as enumerated in the Indian traditional health systems have been shown to have potent immunomodulatory and immune boosting effects\[98] that may be helpful during the infection course. ARDS is a key pathological feature of COVID-19. Terpenoids (such as from neem plant, Azadirachta indica)\[99] and curcumin\[90] are effective in regulating the ARDS in animal models through the inhibition of the NFκB and associated pathways. Therefore, combinations of such natural products may have the potential to be used for prophylaxis and adjunct therapy to treat infected individuals.

Perspective on possible prophylactic measures

Since the spread of COVID-19, a large number of healthcare workers and doctors are directly exposed to the virus and hence susceptible to infection. To prevent spread of the virus in the general population as well, the currently available prophylactic measures are limited to reduction of contact with infected individuals, sanitisation and quarantine measures. However, there is a case to be made for drug prophylaxis. Such prophylactic treatments and vaccinations are commonplace during travel to areas where certain diseases are endemic. For example, chloroquine treatment is started prophylactically a week (500 mcg/week) before travel to areas where malaria is common. Nafamostat\[101] and camostat\[102] are used prophylactically to prevent pancreatitis. Anti-retroviral therapies are used prophylactically\[103] to treat individuals at risk of contracting HIV. Therefore, we discuss here the various kinds of prophylactic options that may be followed in case of COVID-19.

The first group of prophylactic agents may consist of drugs that can inhibit the viral entry and genome release processes required for a successful infection. These include viral uptake receptor antibodies (ACE2 blocking antibodies, ARBs), competitive blockers of viral uptake (such as soluble ACE2), inhibitors of endocytosis and viral genome release (such as chloroquine – Table 1) and replication (such as Ribavirin) etc., It is interesting to note that Curcumin has been shown in vitro to inhibit the enveloped RNA viruses such as Zika and Chikungunya viruses\[96] which may also be applicable to its mode of action against the SARS coronavirus family.\[95] The second group of prophylactic agents may constitute of factors that enhances the anti-viral host immune response such as Imiquimod (imidazoquinolinamines) that enhance the secretion of type I interferon response\[106-108] The potential prophylactic strategies to prevent SARS-CoV-2 infection is summarized in Fig. 3 and Table 1.
In conclusion, we illustrate the variety of potential therapeutic options currently available to us in the face of this incredible threat to human life. Most of the therapeutic options outlined have not undergone intensive pre-clinical and clinical testing, since, SARS-CoV-2 has not allowed scientists and clinicians that luxury. Yet, each of these various discussed modalities have merit in part due to their known activities, and in part due to the known mechanism of the viral infection course. Hence, all these modalities should be carefully considered in the right context at the time and duration of application.

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Conflicts of interest
There are no conflicts of interest.

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