Review Article

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A REVIEW ON POSSIBLE PHARMACOLOGICAL OPTIONS AGAINST COVID-19 IN INDIA

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ABSTARCT
As the whole world is currently facing a public health emergency due to spread of Coronavirus causing Severe Acute Respiratory Syndrome 2 (SARS-CoV-2).Every country is concerned about the pandemic of COVID-19.This new disease and its virus is something which the human race has never faced before and hence it is difficult to find specific treatment for it.Around the globe , a few candidates have shown efficacy in vitro studies, pre clinical trials and some drugs have also shown efficacy in clinical practice however not a single drug has proven effective in large scale randomized clinical trials.This review summarizes the ongoing advances and clinical trials in India dedicated towards designing the therapeutics against COVID-19.The whole world awaits for the results of these clinical trials.

KEYWORDS: COVID-19, coronavirus, pharmacotherapy, treatment.

INTRODUCTION

The coronavirus disease (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2). The first case of COVID-19 reported in late December, 2019, and more patients reported with the same disease over the following days. Although, the epicenter of this disease was located in Wuhan, China.[1] The disease spread rapidly outside of China to the whole world through human transmission by respiratory droplets and eventually the World Health Organization declared a pandemic on March 11, 2020.[2] Now it has spread to more than 180 countries. The first case of COVID-19 in India was reported on 30 January 2020. As of 9 June 2020, India has a total of 266,598 cases, 129,215 recoveries (including 1 migration) and 7,466 deaths in the country. India currently has the largest number of confirmed cases in Asia, with the number of total confirmed cases breaching the 100,000 mark on 19 May and 200,000 on 3 June.[3]
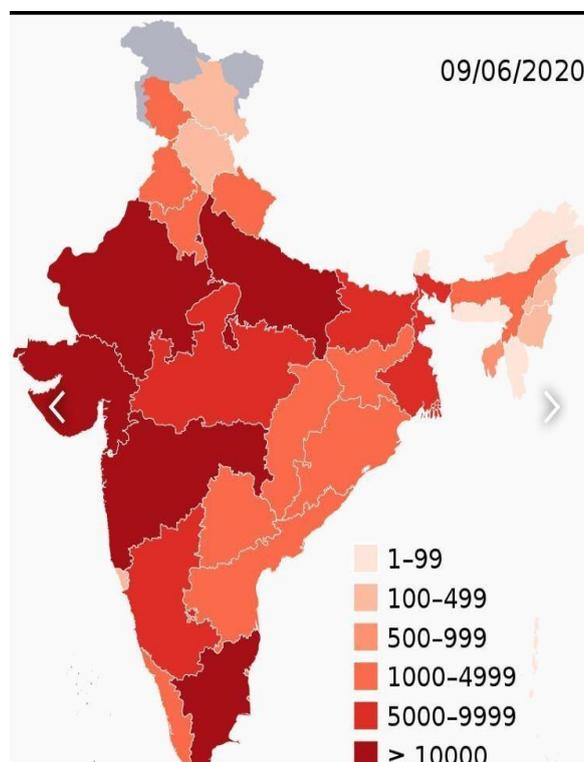
The number of cases and the death rates are still increasing. It has been reported that the most severe cases and mortality are associated with co-morbidities. The most common associated underlying health conditions are diabetes mellitus, pulmonary disease, and

old age.[5] Since SARS- Cov-2 is a newly discovered pathogen, there is no specific drug or vaccine available to date. The researchers and the scientific community have been racing to find the best possible treatment for COVID-19 to save the lives.The current situation demands urgent treatment against COVID-19.

Many treatment options have been proposed, and it has been thought that already existing drugs can be repurposed for use in the treatment of COVID-19. The status of approval or not of a clinical drug trial is determined by Drugs Controller General of India (DCGI).It is a department of the Central Drugs Standard Control Organization of the Government of India.[6] Several drugs like Chloroquine, Hydroxychloroquine, Ivermectin, BCG, Lopinavir, Ritonavir, and Tocilizumab, and many other drugs are under trials to determine the efficacy and safety against COVID-19 treatment in India. In this review, we have summarized available data on Ivermectin, Hydroxychloroquine, BCG, Convalescent Plasma Therapy and other such drugs for the use against COVID-19 and undergoing clinical trials on these drug against COVID-19 in India.[7]

Hydroxychloroquine & Its Combinations

Chloroquine is an antiprotozoal drug used to treat malaria, and Hydroxychloroquine (HCQ) is an analog of Chloroquine used in the treatment of common medical conditions, especially in rheumatoid arthritis and prophylaxis for malaria. Chloroquine has also been considered as a potential drug against COVID-19.[8] Chloroquine acts via elevating the endosomal ph and interferes with ACE2 glycosylation. Hydroxychloroquine has also shown efficacy against SARS-CoV-2 in vitro.[9] because it inhibited the viral activity in vitro study. It also decreases progression to ARDS in patients with severe pneumonia by its immunomodulatory effects. Azithromycin (AZT) has also been shown to have antiviral activity especially against Ebola and Zika viruses. AZT induces antiviral responses in bronchial epithelial cells. AZT decreases viral replication of rhinovirus.[10] The combination of HCQ +AZT has proven to be effective in Ebola. SARS Cov-2 clearance has been demonstrated in patients administered a combination of HCQ +AZT. If efficacy is proven, then early treatment will decrease infectivity of cases and also lead to quicker recovery which will decrease burden on healthcare facilities.

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
1	CTRI/2020/03/024402	N/A	COVID	Hydroxychloroquine	Drug - Hydroxychloroquine {icmr regime} Comparative agent - Hydroxychloroquine usual dose	Phase 3	500
2	CTRI/2020/04/024773	Approved	COVID	Hydroxychloroquine	Drug – Chloroquine or Hydroxychloroquine Drug - Lopinavir with Ritonavir (ditto) plus Interfero Drug - Lopinavir with Ritonavir (orally twice daily for 14 days) Drug - Remdesivir Comparative agent - Local standard of care	Phase 3	1500
3	CTRI/2020/05/025067	N/A	COVID	Hydroxychloroquine Prophylaxis	Drug -Hydroxychloroquine along with Standard care Personal protective equipment Comparative agent - Standard care Personal protective equipment	N/A	10990
4	CTRI/2020/05/025010	N/A	COVID	Hydroxychloroquine Prophylaxis		N/A	2000
5	CTRI/2020/04/024948	N/A	Moderate COVID	Hydroxychloroquine	Drug - Ciclesonide Drug - Hydroxycholoquine Drug - Ivermectin Comparative agent - Standard of Care	Phase 2	120
6	CTRI/2020/05/024982	N/A	COVID	Hydroxychloroquine + Azithromycin		N/A	50
7	CTRI/2020/04/024904	Not Yet	COVID	Hydroxychloroquine	Drug - Hydroxychloroquine	Phase	300

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
		Recruiting		+ Azithromycin	High dose	3	
8	CTRI/2020/05/025022	Not Yet Recruiting	COVID	Hydroxychloroquine	Drug - Hydroxychloroquine Comparative agent - Symtomatic Treatment	Phase 2	166
9	CTRI/2020/05/025242	Not Yet Recruiting	COVID	Hydroxychloroquine sulphate	Drug - Hydroxychloroquine	N/A	400

The first trial of Hydroxychloroquine prophylaxis was done on 31/03/2020 with 500 healthy volunteers working at a tertiary care centre in Kerala. Thereafter trials on use of hydroxychloroquine in combination with Lopinavir, Ritonavir, Interferons was done with 1500 patients thereafter it's use as prophylaxis for COVID-19 was done on large scale for 10990 patients.Subsequently trials were done with varying combinations for over 500 patients. One recent trial on 300 participants with following three regimens (1) standard dose (HCQs) alone, (2) Hydroxychloroquine and Azithromycin (AZT), (3) Hydroxychloroquine in high dose (HCQh) , suggested that addition of Azithromycin(AZT) to normal Hydroxycholoroquine regimen give more superior results. Although efficacy of Hydroxychloroquine has been observed in clinical practice, it has not proven effective in large clinical trials yet, and the results of these trials are awaited. The clinical trials on Hydroxychloroquine are given in above table.

Convalescent Plasma
Blood group matched convalescent Plasma (COVID Plasma) from recovered COVID-19 patients contains antibodies against COVID-19 which may be beneficial to moderate, severe and severely sick(life threatening conditions)COVID-19 infected patients fitting eligibility criteria.[11] It is hypothesized that the use of convalescent plasma will limit the progression of disease in patients with moderate, severe, severely sick COVID-19 infection.

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
1	CTRI/2020/04/024804	Open To Recruitment	COVID	Convalescent plasma	Drug : Convalescent Plasma IV Comparator Agent : Standard Care of Therapy	Phase 1/2	24
2	CTRI/2020/05/025346	Not Recruiting	Severe COVID	Convalescent Plasma	Drug : Convalescent Plasma Comparator Agent : Standard Care of Therapy	N/A	90
3	CTRI/2020/04/024706	Completed	Severe COVID	Convalescent Plasma	Drug : Convalescent Plasma IV Comparator Agent : Random Donor Plasma	Phase 2	40
4	CTRI/2020/04/024775	Not Recruiting	Moderate COVID	Convalescent Plasma	Drug : Convalescent Plasma Comparator Agent : Standard Care of Therapy	Phase 2	452
5	CTRI/2020/05/025209	Approved & not recruiting	Severe COVID	Convalescent Plasma	Drug : Convalescent Plasma Comparator Agent : Standard Care of Therapy	Phase 2	80
6	CTRI/2020/05/025328	Approved & not recruiting	Severe / Very Severe COVID	Convalescent Plasma	Drug : Convalescent Plasma Comparator Agent : Standard Care of Therapy	Phase 2	100
7	CTRI/2020/05/025299	Not Yet Recruiting	COVID	Convalescent Plasma	Drug - Convalescent Plasma Comparative Agent - COVID standard treatment	Phase 2	20
8	CTRI/2020/04/024915	Not Yet Recruiting	COVID	Convalescent Plasma	Drug - Convalescent Plasma Comparative Agent - Standard care of treatment	Phase 2	100

The first trail for Convalescent Plasma therapy occurred on 21/04/2020 on 40 severely and very severely ill patients in Delhi. Consent was taken from patient and plasma was obtained from Recovered patients of COVID-19 under ICMR Protocol. Results of the Convalescent Plasma therapy were compared with Standard supportive care given to the other patients and outcomes were notified on regular basis on day 0 , 3 , 7 day after Convalescent Plasma treatment and followed up for 3 months. The primary outcome is a composite measure of the avoidance of Progression to severe ARDS (P/F ratio <100) or all cause mortality at 28 day. A recent trail of Convalescent plasma therapy vs. Standard Care occurred on 1st June 2020 on 452 patients. Although Efficacy of Convalescent plasma therapy has been observed in clinical practice but not proven effective in large clinical trial yet and result of these trails are awaited. The clinical trials for Convalescent plasma Therapy are given above .

BacilleCalmette-Guérin (BCG)/BCG VPM1002 vaccine
BacilleCalmette-Guérin (BCG) is a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus, Mycobacterium bovis.BCG is known to induce a potent Th1-type response (in particular to increase IFN-gamma) and promote the production of both Th1- and Th2- type cytokines in response to unrelated vaccines.In the latter case, it is likely, however, that BCG stimulates general immune response. This results in faster response to infections that could reduce severity of disease and lead to faster recovery. Overall, BCG vaccine reduces the risk of pulmonary and extra-pulmonary tuberculosis (TB)it has efficacy against TB meningitis and disseminated TB disease. BCG vaccine also provides some protection against leprosy, Non-tuberculous mycobacterial infections and also in superficial carcinoma of the bladder.

It has been shown to reduce severe respiratory distress in children from Africa and conferred beneficial immunity and favorable outcomes to malarial infections. One of the most common side effects of BCG vaccinations are local complications (injection site reactions and suppurative or non-suppurative lymphadenitis).[1]Miller et al, 2020 show a negative correlation between BCG Immunization status of a country and mortalities due to COVID-19. In particular, Miller et al., 2020 have presented epidemiological data that suggests that BCG could be effective against nCoV-19 or SARS-CoV-2.

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
1	CTRI/2020/05/025013	Not Recruiting	COVID	BCG	Drug : BCG Comparator Agent : Saline	Phase 2	60
2	CTRI/2020/04/024749	Approved & open to recruitment	COVID	BCG VMP1002	Drug : Recombinant BCG Vaccine , VPM1002 Comparator Agent : Placebo , 0.9% NaCl	Phase 3	5946
3	CTRI/2020/04/024833	Not yet Recruting	COVID	BCG-Denmark	Drug : BCG-Denmark Comparative agent - Placebo	N/A	1826

The data (yet to be peer reviewed) found that countries that do not have a BCG immunization policy have more COVID-19 deaths and cases. On basis of these data 1st trial on efficacy of Recombinant BCG Vaccine (VPM1002) started in India in April 2020 with 5946 volunteers, and second trial on efficacy of BCG-Denmark stared in April with 1826 volunteers. Another randomized controlled trial on BCG vs. placebo with 60 volunteers started in May 2020.Although BCG has not proven effective in large clinical trials yet, and the results of these trials are still awaited. Table with details of different BCG trials is given above.

Ivermectin
Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero- hSLAM cells 2 hours post infection with SARSCoV-2 able to affect about 5000-fold reduction in viral RNA at 48 h Ivermectin is a CDSCO approved drug. However, it requires further investigation for possible benefits of COVID-19 patients and further eradication of COVID-19 virus.

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
1	CTRI/2020/04/024858	Not Recruiting	COVID	Ivermectin	Drug : Ivermectin Comparator Agent : Standard Care of Therapy	N/A	50
2	CTRI/2020/05/025224	N/A	COVID	Ivermectin	Drug : Ivermectin Comparator Agent : Standard Care of Therapy	Phase 2	50

3	CTRI/2020/04/024948	Not Recruiting	COVID	Ivermectin	Drug - Ciclesonide Drug - Hydroxychloroquine Drug - Ivermectin Comparative agent - Standard of Care	Phase 2	120
4	CTRI/2020/05/025068	Not Recruiting	COVID	Ivermectin	Drug - Ivermectin Comparative agent : Standard Treatment	Phase 3	50
5	CTRI/2020/05/025333	Not Recruiting	COVID	Ivermectin	Drug - Ivermectin	Phase 2	2000

The first trail for Ivermectin occurred on 25/04/2020 on 50 confirmed patients of COVID-19.This study aims to confirm the antivirus effectiveness of Ivermectin on coronavirus i.e. COVID 19 then to explore its potential use in the combating to the COVID 19 pandemics.. Viral load will be monitored at 1, 3 & 5 days from beginning of trial drug vs. Standard care of treatment .The primary outcome is Safety of the drug and eradication of virus. Another recent interventional trail occurred on 27th May 2020 with 2000 Confirmed COVID-19 cases on use of Ivermectin as Prophylaxis for COVID-19 pandemics. Although Efficacy of Ivermectin has not been proven yet but many clinical trial have undergone for it and results of these trail are awaited. The clinical trials for Ivermectin are given above.

Other Trials
1. **Itolizumab**:- It is a humanized anti-CD6 monoclonal antibody. When administered, it acts as an antibody which can restore the immune system's attack on foreign bodies. Itolizumab is used to treat a skin condition called psoriasis and is now being tried on COVID -19 patients through clinical trials.
2. **Topical nasal Chloroquine:-** The drug possibly prevents an over-activation of the immune system and therefore permits a more efficient viral clearance. Other scientists point to work done with the original SARS virus that suggests chloroquine alters glycosylation, a process of decorating proteins with unique patterns of sugar. The virus's spike proteins, which it uses to grab onto cells and begin its infiltration, are glycosylated, so interfering with this process may prevent newly created viruses from infecting other cells.
3. **Anti viral combination therapy**:- Lopinavir has inhibited viral replication by blocking the proteases of the SARS-CoV-1 in-vitro study. Lopinavir/ribavirin inhibited the viral replication after forty-eight hours of the incubation period.[14] The effective concentration (EC50) Young et al. reported that five out of 18 patients was observed in Vero cells against SARS-CoV-1. Lopinavir is used in combination with ritonavir against HIV.
4. **Oral Niclosamide**:Niclosamide (NIC) is a potential drug against COVID-19. Prevention of viral entry by altering endosomal pH and prevention of viral replication by inhibition of autophagy are the plausible mechanisms of NIC against COVID-19. Clinical efficacy of NIC against COVID-19, therefore, need to be evaluated against COVID-19.[15,16,17]
5. **Favipiravir**:- Favipiravir has broad-spectrum antiviral activity, and it acts as an alternate substrate in viral replication, which results in inhibition of viral replication. Favipiravir has also demonstrated efficacy against SARS-CoV-2 in vitro study.It is also used against Ebola virus. .Favipiravir is also under trials to determine the efficacy against COVID-19.[18]
6. **Cytokine Cocktail:** The treatment technique simply involves stimulating the immune responses in the early stages of COVID-19. They have made a concoction of cytokines – IF-gamma, along with cytokines which are released by our immune system against the virus attack and have been known to be effective against COVID-19 too[19].
7. **Losartan:** It acts by blocking ACE-2 receptors, which have been proven to be the doorway novel coronavirus uses to gain entry to cells, but most recent studies have warned of more severe infections. Thus it may not help acutely in COVID infections, but will bring long term changes in the management of infections in patients with chronic diseases.[20]
8. **Tocilizumab**:- It act against membrane-bound and soluble interleukin-6 (IL-6) receptors which are secreted by immune cells of the body in response to inflammation. It has been reported that a surge of IL-6 has been observed in severe cases of COVID-19 as well as in those patients who could not survive. It is also used against Rheumatoid Arthritis.[21]
9. **Resveratrol-copper tablet**:- Deadly Coronavirus results in inflammatory reaction via activation cytokines IL-6 and TNF thus In addition to inhibition of viral replication, blunting the inflammatory response before overt cytokine storm is important to improve outcomes. The polyphenol , resveratrol, a potent antioxidant that has shown antiviral activity against several viruses.[22]
10. **Melatonin**:- Melatonin enhances the production of progenitor cells of granulocyte , macrophage and natural killer cells , increases production of IL2,IL6,IL12 and increases helper T cells. It can reverse immunosenescence of old age and immunocompromised states and prevent them from COVID-19 related disease.[23]
11. **2-Deoxy D Glucose :-** 2-Deoxy D Glucose (2-DG)

can dock efficiently with viral main protease 3CLpro as well as NSP15 endoribonuclease, thus efficiently inactivating these viral receptors leading to incapacitation of the SARS-CoV-2 virus.

12. Imatinib:- Imatinib is a tyrosine kinase inhibitor. It is reported that kinase signaling may be important for replication of two members of the Coronaviridae family, SARS-CoV and MERS-CoV.

In vivo studies performed in the mouse model of vaccinia virus infection showed that imatinib was effective in blocking dissemination of the virus.[24]

NO.	Clinical Trial ID	Status	Condition	Drug	Intervention	Phase	Sample Size
1	CTRI/2020/05/024959	N/A	COVID	Itolizumab	Drug : Supportive care with Itolizumab Comparative agent : Supportive care which includes antivirals /antibiotics/ hydroxychloroquine; oxygen therapy	Phase 2	30
2	CTRI/2020/04/024729	Not Recruiting	COVID	Topical Nasal Chloroquine	Drug : Topical Nasal 0.03% chloroquine eye drops Comparative Agent : Standard Treatment	Phase 2	60
3	CTRI/2020/06/025575	N/A	COVID	Anti-viral combination Therapy	Drug : Hydroxychloroquine, Ribavirin, ST-NS Drug : Hydroxychloroquine, Ribavirin, ST-S Drug : Lopinavir, Ritonavir, Ribavirin, ST-S Comparative agent : Standard Treatment(STns) Comparative agent : Standard Treatment(STs)	Phase 3/4	175
4	CTRI/2020/04/024949	N/A	Very Mild / Mild COVID	Oral niclosamide	Drug : Niclosamide 500 mg Comparative agent : Standard of care only	Phase 2	48
5	CTRI/2020/05/025114	Approved & open to recruitment	COVID	Favipiravir	Drug : Favipiravir 200mg Tablets Comparative agent : Standard Supportive Care	Phase 3	150
6	CTRI/2020/05/025432	Approved & not recruiting	COVID	Cytokinin Cocktail	Drug : Cytokine Cocktail Therapy containing Interferon Gamma	Phase 1	6
7	CTRI/2020/05/025319	Not Yet Recruiting	COVID	Losartan	Drug : Losartan Comparator Agent : Placebo	Phase 3	186
8	CTRI/2020/05/025369	Not Yet Recruiting	COVID	Tocilizumab	Drug : Tocilizumab Comparator Agent : Standard Care of Therapy	Phase 3	180
9	CTRI/2020/05/025336	Not Yet Recruiting	COVID	1. Resveratrol-Copper tablets 2. Chlorophyllin tablet	Drug : Chlorophyllin Tab Drug : Resveratrol-Copper Tab Comparator Agent : Standard Care of Therapy	Phase 3	300
10	CTRI/2020/05/025337	Not Yet Recruiting	COVID	1. Resveratrol-Copper tablets 2. Chlorophyllin tablet	Drug : Chlorophyllin Tab Drug : Resveratrol-Copper Tab Comparator Agent : Standard Care of Therapy	Phase 2	200
11	CTRI/2020/06/025613	Not Yet Recruiting	COVID	Melatonin	Drug : Melatonin Comparator Agent : Placebo	Phase 4	200
12	CTRI/2020/06/025664	Not Yet Recruiting	COVID	2-Deoxy-D-Glucose	Drug : 2-Deoxy-D-Glucose Oral Powder Comparator Agent : Standard Care of Therapy	Phase 2	40
13	CTRI/2020/04/024806	Open To Recruitment	COVID	Imatinib	Drug : Imatinib Oral Comparator Agent : Standard Care of Treatment	Phase 2	100

These drugs are under trial, some of the drugs like Imatinib showed clinical benefits .In view of requirement of long term period to develop a targeted anti-viral response, there is a need of repurposing already available drugs, that have in-vitro anti-viral activity. Imatinib is one such drug which has inhibitory activity in early phases of SARS and MERS corona virus infection, studied in-vitro. While the rest of them are still under study like Itolizumab.It is an investigational drug, the benefit to COVID-19 patients experiencing complications such as Cytokine Release Syndrome is not known. However, findings from this study may be beneficial to the society at a large at the National and International Level.

CONCLUSION
The proper evaluation and appropriate management techniques against COVID-19 are rapidly evolving. The best possible regimen to treat the infection or to prevent the disease progression to critical is still challenging. Many drugs listed in this article are encouraging, and even some candidates have shown efficacy in clinical practice in India. However, the potential benefit of the therapy on a large-sized population is yet to determine. There should be a well-defined strategy for those patients who warrant therapy. The timing of initiation of therapy and dosing of therapy is also considered important. The rapid initiation of therapy should be considered in all those patients who are hospitalized either in the context of ICMR guidelines or randomized controlled clinical trials. The researchers are struggling hard for an effective and potential candidate to control the COVID-19 effectively. As there is no potent medicine available to date against COVID-19, we have to rely on measures, especially strict preventive and control measures, which might help in minimizing the risk of disease spread. The current situation demands urgent treatment for COVID-19. Safety and efficacy related data from the highly randomized controlled clinical trials are needed. Meanwhile clinical drug trials of Remdesivir, Ruxolitinib, Mefloquine, Aslopinavir, Ravulizumab and many other drugs have occurred on a large scale in different parts of globe, India is also intending to start those trails soon.

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