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Review on COVID-19: a recommendation to examine the effect of different medicine and herbs in preventing infection and progression

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Abstract

More than 199 countries worldwide are affected by a new coronavirus disease (COVID-19) caused by infection with SARS-CoV-2gh21. The transition from early symptoms to acute respiratory distress syndrome (ARDS) is most likely due to uncontrolled cytokine release. There is an urgent need to identify safe and effective drugs for treatment. Many drugs exhibit a promising inhibitory effect. However, the clinical use of some medications can cause serious side effects. We proposed that natural herbs could serve as a better therapeutic approach.

Introduction

A new pathogen, identified as a novel coronavirus (SARS-CoV-2), triggered a new outbreak of pneumonia (COVID-19) in December 2019, starting in Wuhan, China, and is rapidly spreading to 31 provinces in China and over 199 countries all over the world. SARS-CoV-2 is a beta coronavirus and shares the genetic sequence and viral structure with the acute respiratory syndrome corona virus (SARS-CoV; 70% similarity), which caused 349 deaths in 2002-2003 in China and Middle East Airway Corona Virus Syndrome (MERS-CoV; 40% similarity). As of March 4, 2020, a total of 1,130,933 confirmed cases of COVID-19 had been reported, including 60,150 deaths in all over the world. An increasing number of COVID-19 cases have also been reported in the United States, Spain, Germany, Iran, Japan, South Korea and Italy.

The number of COVID-19 cases continues to increase. The median time from first symptoms to ARDS is 8 days (IQR 6-12 days). The transition to ARDS occurs in many severe cases of COVID-19. A possible explanation for this rapid and severe deterioration is cytokine release syndrome (CRS), or "cytokine storm," an overproduction of immune cells and cytokines that leads to rapid failure of the multi-organ system and fetal damage to tissues i.e. lungs, kidney and heart. Developing an effective approach to modulate the immune response or suppress the production of reactive cytokines is of crucial importance in reducing disease aggravation and mortality rate. There is an urgent need to identify effective and safe medical agents to treat this disease[1].

CORONA VIRUS LIFE CYCLE

The life cycle of the corona virus (Fig. 1) is summarized below to provide a context for the discussion of the functions of various viral proteins. Corona viruses bind to specific cellular receptors through the spike protein, triggering a conformational change in the spike that then mediates fusion between the viral and cellular membranes, resulting in the release of the nucleocapsid into the cell. Upon entry into the cell, the 5 'end of the genome RNA, ORFs 1a and 1b, are translated into pp1a and pp1ab; pp1ab is translated through a frame shift mechanism, which occurs at high frequency (25-30%). ORF 1a encodes one or two papain-like proteases (PLpro or PLP) and a 3C picornavirus-like pro

-tease (3CLpro), which function to process pp1a and pp1ab in mature replicase proteins. Furthermore, encoded in the X domain of ORF 1a is an (assumed) ADP-ribose 1 "-phosphatase activity. Encoded in ORF 1b and processed from pp1ab there is an RNA-dependent RNA polymerase (RdRp) and a helicase, as well as other enzymatic activities, including a (putative) 3 'to 5' exonuclease (ExoN), poly (U) -specific endoribonuclease (XendoU), and (putative) S-adenosylmethionine-dependent ribose 2'-O-methyltranferase. An additional putative enzyme activity, cyclic phosphodiesterase, is encoded downstream in ORF 2a. These multiple enzyme activities are speculated to play roles in coronavirus RNA metabolism and / or interference with host cell processes[2].

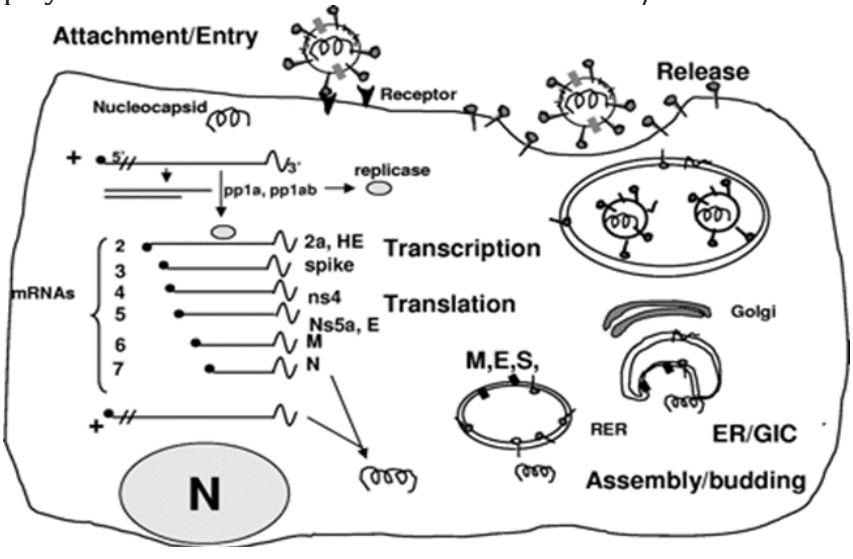

Fig1: Coronavirus replication model. After receptor interaction and fusion of viral and plasma membranes, virus-specific proteins and RNA are synthesized, probably entirely in the cytoplasm. Coronavirus expression begins with the translation of two polyproteins, pp1a and pp1ab, that undergo cotraductional proteolytic processing in the proteins that form the replicase complex. This complex is used to transcribe a 3'-coterminal set of nested subgenomic mRNAs, as well as genomic RNAs, that have a common 5 'leader' sequence derived from the 5 'end of the genome. Proteins are translated from the 5 'end of each mRNA. The new virions assemble by sprouting into the intracellular membranes and are released through the vesicles by the mechanisms of cell secretion. RER, rough endoplasmic reticulum; ER / GIC, endoplasmic reticulum / Golgi intermediate compartment.

Treatment by targetting issue1

1. Inhibiting SARS-CoV-2 replication in cell culture.
2. Treating MERS and SARS in animal models.
3. Inhibit lysosomal activity in antigen presenting cells (APCs) including plasmacytoid dendritic cells (pDCs) and B cells.
4. Reduces T cell activation.
5. Inhibit cytokines produced by T cells and B cells (e.g. IL-1, IL-6 and TNF).
6. Interrupted binding between toll-like receptors (TLR7 and TLR9) and their RNA/DNA ligands.
7. Interferes with the interaction between cytosolic DNA and the nucleic acid sensor cyclic GMP-AMP (cGAMP)
8. synthase (cGAS).
9. Interfering with the glycosylation of Angiotensin-Converting Enzyme-II (ACE-II)
10. Blocking virus fusionwith the host cell.
11. Reduce the binding efficiency between ACE-II on host cells and the SARS-CoV spike protein by inhibiting Lysosomal proteases activity.

Medicines and herbs can be used for pre and post COVID-19 infection.

It is reported that various drugsbelongs to the category of Antiviral, Antimalarial, Anti-HIV,Antibiotic macrolides and Anti-rheumatic drugsare ide the treatment of Covid -19. These herbs could have potential effect on Covid-19 disease. Some medicinal agentswith their recommended doses are summarized below (Table 1).

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Table1. Reported Medicinesfor the treatment of COVID-193

S. No.	Category Name	Medicament/ Chemical Name	Inhibitory Mechanism	Dosage
1.	ANTIVIRAL AGENTS	Baloxavir	No data to date support use in the treatment of COVID-19	One registered Chinese trial (2000029548) specifies a baloxavirmarboxil dosage of 80 mg orally on day 1, 80 mg orally on day 4, and 80 mg orally on day 7 as needed, not to exceed 3 total doses.
		Remdesivir ***Updated on 24/03/20***	Broad-spectrum antiviral with activity against coronaviruses Previously tested for SARS, MERS, and Ebola; In vitro evidence of activity against SARS-CoV-2	Phase 3 trial protocol (severe COVID-19): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2)
		Oseltamivir	Antivirals active against influenza viruses Neuraminidase inhibitors	Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours.
2.	ANTIMALARIAL	Chloroquine Phosphate ***Updated on 27/03/20***	Active against SARS-CoV-1 and MERS-CoV(in-vitro) Immuno-modulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections	Various dosages recommended or being investigated **Oral chloroquine phosphate:** 500 mg twice daily for 10 days **Oral chloroquine phosphate:** 500 mg twice daily for 7 days (adults 18-65 years weighing >50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing<50 kg) **Oral chloroquine phosphate**: Initial dose of 600 mg (chloroquine) upto12 hours; later on day 1, then 300 mg (of chloroquine) twice daily on days 2-5
		Hydroxychloroquine (Plaquenil®) ***Updated on 27/03/2020***	In vitro activity against SARS-CoV-2 in infected Vero 6 cells reported; may be more potent than chloroquine invitro, but some data are conflicting and additional study needed Immuno-modulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections	Various dosages recommended or being investigated **Oral hydroxychloroquine sulfate:** 400 mg twice daily on day 1, then 200 mg twice daily on days 2- 5 **Oral hydroxychloroquine sulfate:** 400 mg once or twice daily for 5-10 days **Oral hydroxychloroquine sulfate:** 600 mg twice daily on day 1, then 400 mg daily on days 2-5 **Oral hydroxychloroquine sulfate:** 100-200 mg twice daily for 5-14 days **Oral hydroxychloroquine sulfate:** 200 mg 3 times daily for 10 days
3.	ANTI HIV DRUG	Lopinavir and Ritonavir (LPV/RTV; Kaletra®) ***Updated on 24/03/20***	HIV Protease Inhibitor Antiretroviral with in vitro activity against SARS-CoV and MERS-CoV; some evidence of benefit in animal studies for treatment of MERS-CoV	**COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily for 14 days **COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily with or without arbidol (200 mg every 8 hours) for up to 21 days **COVID-19:** LPV 400 mg/RTV 100 mg orally with or without interferon (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile
				water by nebulization) and with or without ribavirin for up to 10 days **SARS:** LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours) **MERS:** LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α ; LPV 400 mg/RTV 100 mg orally twice daily with interferon β1b (0.25 mg/mL subQ on alternate days) for 14 days
4.	ANTIBIOTIC MACROLIDES	Azithromycin ***Added 24/03/2020***	Antibacterial with some in-vitro activity against some viruses (e.g., influenza A H1N1, Zika) No data to date on in-vitro activity against corona-viruses, including SARS-CoV-2 Immuno-modulatory and antiinflammatory effects, including effects on pro-inflammatory cytokines; precise mechanisms of such effects not fully elucidated.	**Adjunctive treatment in certain viral infections:** 500 mg once daily has been used
5.	ANTI-RHEUMATIC DRUG	Sarilumab (Kefzara®) ***Updated 27/03/2020***	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine re-lease syndrome (CRS) and pulmonary symptoms in severely ill patients.	Not available (see Trials or Clinical Experience)
		Tocilizumab (Actemra)	Used as a treatment of cytokine release syndrome (CRS) that is severe or life-threatening.	IV infusion: **China** recommends an Initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as ini-tial dose) after 12 hours. No more than 2 doses should be given; maxi-mum single dose is 800 mg.

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It is also recommended that some supportive agents are also assist in prevention or cure from COVID-19 infection. Such agents are listed in table 2.

Table 2: Supporting agents can be used in the treatment of covid-19 Table3

S. No.	Category Name	Medicament / Chemical Name	Inhibitory Mechanism	Dosage
1.	*Vitamin*	Vitamin C Ascorbic acid ***Added 24/03/2020***	Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress.	Phase 2 trial protocol: Ascorbic acid 12 g IV every 12 hours for 7 days (12 g of drug diluted in sterile water for injection to total volume of 50 mL and infused IV at rate of 12 mL/hour)
2.	Steroids	Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®)	Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia	Based on expert consensus statement from Chinese Thoracic Society, dosage of methylprednisolone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent). [7] Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days.
3.	Vasodilating agent	Nitric oxide (inhaled)	Selective pulmonary vasodilator; may be useful in the treatment of acute	Inhaled nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and
		Updated 24/03/2020	respiratory distress syndrome (ARDS), a potential complication of COVID-19.	10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) in a pilot study in SARS-CoV patients
4.	Disease modifying Anti-rheumatic Drug	Sarilumab (Kefzara®) ***Updated 27/03/2020***	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine re-lease syndrome (CRS) and pulmonary symptoms in severely ill patients.	Not available (see Trials or Clinical Experience)
		Tocilizumab (Actemra®) ***Updated 24/03/20***	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine re-lease syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients.	IV infusion: **China** recommends an Initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg [2]
5.	Immuno-suppres-sive agent (mTOR inhibitor)	Sirolimus	mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including corona-virus.	Dosage of sirolimus in the open-label trial was 2 mg daily orally, administered in conjunction with oral prednisolone 20 mg daily for 14 days; patients also received oseltamivir 75 mg twice daily for 10 days
6.	Non-steroidal Anti-inflammatory Agents (NSAIA)	Indomethacin	Possible antiviral activity against othercorona viruses SARS-CoV& Canine-CoV (interferes with viral RNA synthesis.	No data to date support use in treatment of COVID-19
7.	Chemical salt	Ammonium Chloride (NH_4Cl)[4]	Use as a lysosomotropic agents (increase the lysosomal pH) and also inhibit the glycosylation of ACE2.	Combination of Chloroquine (50μM) with Ammonium Chloride (NH_4Cl) 10mM.

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However, none of the data reported regarding the potential activity of herbal drugs either for prevention or cure of such ailment. Thus, the present reviewed the potential herbal counterparts and their activity that could be helpful for protection from such threatening disease. Such potential counterparts are presented in table 3.

Table 3: Herbal Drugs can be used in the treatment of covid-19 Table

S. No.	Category Name	Botanical Name	Medicament /Chemical Name	Inhibitory Mechanism
1.	Oregano[5] (Mint Family)	Origanumvulgare	carvacrol	effective in inactivating MNV within 1 h of exposure by acting directly on the viral capsid and subsequently the RNA.
2.	Basil (Tulsi)[6,7]	Ocimumtenuiflorum	Apigenin and Ursolic acid	used to identify possible antiviral activities against DNA viruses (herpes viruses (HSV), adenoviruses (ADV) and hepatitis B virus) and RNA viruses (coxsackievirus B1 (CVB1) and entero virus 71 (EV71). In a 4-week study in 24 healthy adults, supplementing with 300 mg of holy basil extract significantly increased levels of helper T cells and natural killer cells, both of which are immune cells that help protect and defend your body from viral infections.
3.	Fennel[8]	Foeniculumvulgare	Trans-anethole	effective in inflammatory pain with the antiinflammatory effects of trans-anethole reported to derive from its regulation of NF-κB signaling pathways.
4.	Garlic[9]	Allium sativum	Allicin, Allyl alcohol,diallyltrisulfide and ajoene	garlic extract showed *in vitro* activity against influenza A and B, viral pneumonia by stimulating Protective immune cells. Allyl alcohol and diallyl disulfide have also proven effective against HIV-infected cells
5.	Peppermint[10]	*Menthapiperita*	Phenolic acid and flavonoid	*Menthapiperita* L. leavescontained high levels of phenolic acid and flavonoid, showed antiviral activity against RSV with a high selectivity index, and significantly decreased the production of NO, TNF-α, IL-6, and PGE2 in lipopolysaccharide-stimulated RAW 264.7 cells.
6.	Echinacea[11]	*E. angustifolia, and E. purpurea*	polysaccharides, glycoproteins, alkamides and cichoric acid; the latter is a derivative of *caffeic acid.*	*prevention were illustrated in 2002 with the sudden appearance of the SARS (severe acute respiratory syndrome) pandemic.* *Several herbal extracts have been shown recently to possess a combination of bioactivities that could be useful in the control of colds, flu, and bronchitis and, in retrospect, some of these could have been useful for SARS patients. It works on Influenza virus A (human and avian); influenza B; HSV-1 and -2; coronavirus; respiratory syncytial virus; rhinoviruses.*
7.	Sambucus12,13	Sambucusnigra	Pectin, pectic acid, protopectin, Capectate and cellulose. Glutamic acid,aspargic acid and alanine	As an alternative to antibiotic misuse for upper respiratory symptoms due to viral infections, and a potentially safer alternative to prescription drugs for routine cases of the common cold and influenza. Phenolic compounds from the elderberry fruit extract bind to H1N1 virions, thus blocking their ability to infect host cells. Standardized liquid extract of elderberry (Rubini®) Reduction in the spread of the foci size of influenza B human virus,reduction in the foci of influenza A (KAN-1) human virus in MadinDarbycanine kidney cell culture (MDCK) Elderberry extract:Inhibition of influenza A (H1N1) human virus in MDCK;concentration of 252 μg/mlIC50for H1N1; concentration of 1000 μg/ml100% inhibition of H1N1 Concentrated elderberry juice:Inhibition of H1N1 in MDCK extract concentration of 720 μg/mlIC50for H1N1 (samples were given during infection) Extract concentration of 3600 μg/ml IC50for H1N1 (samples were given immediately after infection) Elderberry extractsInhibition of infectious bronchitis virus (IBV)–a pathogenic chickencoronavirus. Reduction in IBV titers by several orders of magnitude, independence of the dose applied. Elder bark extractHigh activity against feline
				immunodeficiency virus (FIV)–commondomestic cats virus
8.	Licorice[14]	Glycyrrhizaglabra	Glycyrrhizin, liquiritigenin, glabridinGlycyrrhizin, ChalconeandGlycyrrhetinic acid	Licorice root extract is effective against HIV, RSV, herpes viruses, and severe acute respiratory syndrome, which causes a serious type of pneumonia. Reduce HMGB1 binding to DNA, and inhibit influenza virus polymerase activity.
9.	Astragalus[15]	Astralagusmembranaceus	polysaccharides such as contain mannose, D-glucose, Dgalactose, xylose and Larabinose.	The effect on lymphocyte and serum antibody titers *in-vivo* was also investigated. IL-4, IL-6, IL-10, LITAF, IL-12 and antibody titers to H9N2 AIV were enhanced in the first week after APS treatment. The results indicated that APS treatment reduces H9N2 AIV replication and promotes early humoral immune responses in young chickens.
10.	Ginger[16]	Zingiberofficinale	mixture of zingerone, shogaols, and gingerols, volatile oils.	Compounds in ginger also increase levels of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, which may be beneficial in inflammatory reactions triggered by viral infections. Anti-influenza agents have been isolated from *Z. officinale*. TNF-α, reported as antiinfluenza cytokine, has been reported to be present in ginger
11.	Ginseng[17]	Panax ginseng	protopanaxatriol (PT)-typeginsenosides (Re, Rf, and Rg2) and protopanaxadiol (PD)type ginsenosides (Rb1, Rb2, Rc, and Rd)	Ginseng has been reported to have antiviral effects on H1N1, H3N2, and H5N1.
12.	Dandelion[18,19]	Taraxacummongolicum	(believed to have antiinflammatory and anticancereffects).Other related compounds include betaamyrin, taraxasterol, and taraxerol, as well as free sterols (sitosterin, stigmasterin, and phytosterin),	Taraxacummongolicum extract at 1-100 μg/ml markedly inhibited DHBV DNA replication. Additionally, TME at 25-100 μg/ml reduced HBsAg and HBeAg levels and produced inhibition rates of 91.39 and 91.72% at 100 μg/ml, respectively. 0.625-5 mg/ml of dandelion extracts inhibited infections in Madin-Darby canine kidney (MDCK) cells or Human lung adenocarcinoma cell line (A549) of PR8 or WSN viruses, as well as inhibited polymerase activity and reduced virus nucleoprotein (NP) RNA level.
13.	Clove[20]	Syzygiumaromaticum	main source of phenolic molecules like hidroxibenzoic acids, flavonoids, hidroxiphenylpropens, hidroxicinamic acids, and eugenol	The anti-inflammatory effects of eugenol were attributed to its effect to prevent neutrophil/macrophage chemotaxis and prostaglandin synthesis as well as cyclooxygenase II enzyme expressions. Research revealed the antiviral efficacy of S. aromaticum aqueous extracts against herpes simplex virus type 1 (HSV-1) and influenza A virus when combined with acyclovir.
14.	Black pepper[21]	Piper nigrum	Its main alkaloid piperine and ten piperamides	Anti-viral properties against three viruses related to upper respiratory tract infections.

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Formulation may be helpful for pre and post infection of COVID 19 other than Allopathic medicine:

1. **Clove and Black Pepper:** Clove (5 pieces) with Black pepper (15 piece) dry heated on iron plate then make the dry powder. This powder mixed with 2 spoonful honey.

Dose: Complete mixture use in three times in a day.

2. Basil (Tulsi) drop

Dose: 10 drop in 100 ml of water two times.

3. **The lung-clearing and detoxing soup**[22]

Composition of soup: Basil Tulsi (10 leaves), Ginger (2 gm), Fennel (2 Spoonful), Clove (2 piece), Black Pepper (3 piece), kalabansa (4 leaves), Guava (2 leaves), Licorice (1 gm), ajwain (2gm) Betel leaves (1/2 leaves) Cinnamon (1gm), ephedra (1gm). All the medicine dip in one litre of water overnight and boil until 100ml remain.

Dose: 100 ml soup in two times in a day.

4. Continuous using hot water.

5. Blanket using for Corona Virus infected patient in hospital for body temperature increasing.

The above herbal drugs show their effect either by limiting the progressionofCOVID-19 by inhibiting the cytokine storm by reducing CD154 expression in T cells or indicate antiviral effect at both pre and post infection stages. Moreover, Herbal medicine have mild side effects, safer in pregnancy and cheaper also and abundantly scattered in India.

Conclusion:

We have proposed the applications of herbal medicines that could serve as a better therapeutic approach over COVID-19 patients with the allopathic medicine for treatment of SARSCoV-2infection. Potential reasons for this are that herbal drugs can inhibit the progression of COVID-19 or act as an antiviral agent at both pre and post-infection stages. Such agents are common ingredients of Indian origin with no side effects. Thus it is concluded that the given combination if adopted could potentially reduce the fast-growing number of COVID-19 patients.

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