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Treatment trends to the emerging COVID 19 pandemic

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ABSTRACT: In late December 2019, a pandemic named coronavirus disease 2019 (COVID-19) caused by SARS-CoV 2 has taken the global healthcare system into a great dilemma. It affected the country's medical, financial and public health system to a great extent. The disease is mild in most people with symptoms of fever, cough, malaise, throat pain etc., which can later progress into pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction which makes the disease most complicated. In some patients the disease is asymptomatic which may lead to late diagnosis and there by spread in the community. The global pandemic has put pressure on clinicians and The Food and Drug Administration (FDA) to act quickly to make medications in reach of patients. This review aimed to summarize all the treatment options that are currently in practice for the treatment of COVID-19. The review also briefly described the Ayurvedic modalities that are discussed in literature for this pandemic.

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INTRODUCTION:

In late December 2019, a novel coronavirus infection (2019-nCoV) was confirmed in a group of patients with pneumonia of unknown etiology in Wuhan, China [1]. Coronavirus disease 2019 (COVID-19) became a Public Health Emergency of International Concern as declared by The World Health Organization (WHO) [2]. Coronaviruses are enveloped in positive sense RNA viruses ranging from a diameter of 60 to 140 nm, having spike-like projections on its surface giving it a crown like appearance under the electron microscope and hence the name coronavirus [3]. Four corona viruses namely

HKU1, NL63, 229E and OC43 have been in human's circulation, and they generally cause mild respiratory disease [4]. China informed the outbreak to the World Health Organization on 31 December 2019 and the Huanan seafood market closed on 1 January 2020. The virus was identified on January 7 as a coronavirus with >95 % homology to the bat coronavirus and >70 % similarity to the SARS CoV. Environmental samples collected from the Huanan sea food market were also tested positive, signifying that the virus originated from there [5].

There was an exponential increase in the number of cases, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [6]. The first fatal case was reported on 11th Jan 2020.

People of all ages are susceptible infection is transmitted by large droplets formed by symptomatic patients during coughing and sneezing, but canals occur from asymptomatic people and before the onset of symptoms [7]. Studies showed higher viral loads in the nasal cavity compared to the throat, with no difference in viral load between symptomatic and asymptomatic people [8]. Such infected droplets will spread 1 to 2 m over surfaces and deposit.

In favourable atmospheric conditions, the virus can remain viable on surfaces for days, but is destroyed in less than a minute by common disinfectants such as sodium hypochlorite and hydrogen peroxide [9]. Infection is acquired either by inhaling these droplets or by touching contaminated surfaces, and then by touching the nose, mouth and eye. The virus is also present in the stool and water supply contamination, and hypothesizes subsequent transmission via aerosolization / fecal oral route [10].

Clinical Features:

Clinical characteristics of COVID-19 vary from asymptomatic to acute respiratory distress syndrome, and multi-organ dysfunction. Fever (not in all), cough, sore throat, headache, fatigue, anxiety, myalgia, and breathlessness are common clinical characteristics. Conjunctivitis was identified, too. They are thus indistinguishable from other airborne infections. In a subset of patients the disease can progress to pneumonia, respiratory failure, and death by the end of the first week. This development is associated with extreme increase of inflammatory cytokines like IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα [11].Witnessed complications included acute injury to the lungs, ARDS, shock and acute kidney injury. Recovery began in 2ndor 3rd week. For those who survived, the mean period of hospital stay was 10 days. Adverse effects and death are more common among elderly people and those with underlying comorbidities (50 to 75 % of fatal cases) [12].

Diagnosis:

A suspect case is described as one with fever, sore throat and cough that has travel history to China or other areas of frequent local transmission or interaction with patients with similar travel history, or those with confirmed COVID-19 infection. Cases may however be asymptomatic or even without fever. A confirmed case is a suspected case with a molecular test positive.

Specific diagnosis involves specific molecular testing of respiratory samples (throat swab / nasopharyngeal swab/ sputum/ endotracheal aspirates and alveolar broncho-lavage). Virus can also be found in the urine, and blood in extreme cases. In a suspicious case in India, the correct sample has to be sent to specified reference laboratories in India or to the National Virology Institute in Pune.

Other lab investigations are typically unspecific. The count of white cells is usually normal or low. Lymphopenia can occur; serious illness has been associated with a lymphocyte count < 1000. The count of platelets is generally normal or mildly low. CRP and ESR are usually elevated but the levels of procalcitonin are normal.

A high level of procalcitonin may indicate a co-infection with the bacteria. There may be elevated ALT/AST, prothrombin time, creatinine, D-dimer, CPK, and LDH, and high levels associated with serious illness.

The X-ray in the chest (CXR) usually shows bilateral penetration but may be normal in early illness. The CT is more sensitive and specific. CT imaging generally shows infiltration, opacity of ground glass and consolidation of sub segments [13].

Treatment:

Treatment is basically supportive and symptomatic. The first step is to ensure sufficient isolation to prevent exposure to other partners, patients and health-care workers.

The usual principles are to maintain hydration and nutrition and to control fever and cough [12].The WHO has published detailed guidelines for managing critical care for COVID-19 [13].[As far now, no approved treatment for COVID-19 is established but it going to be approved very soon as per the market information.

ANTIVIRALS:

Nucleoside Analogs*:*

Ribavirin, a nucleoside analogue, exhibits antiviral activity against some animal CoVs, and many patients were treated with Ribavirin along with corticosteroids in the SARS-CoV outbreak and became a standard treatment regimen for SARS-CoV. Lack of control group, however, impeded the true effect size. Again, Ribavirin efficacy against SARS-CoV was not demonstrated by *in-vitro* testing. Many patients on the combination of Ribavirin and corticosteroid also showed a rise in viral load after treatment. Consequently its use decreased over a period of time [14]. The doses needed for SARS antiviral activity vary from 1.2 to 2.4 g by mouth per 8 h which are associated with severe patient toxicity [15].

Despite the limitations of poor data, Chinese guidelines recommend Ribavirin 500 mg IV 2 to 3 times daily in combination with LPV / r or inhaled interferon-α (5 million units nebulized twice daily) as one of the standard treatment options for COVID-19. Interferon (α, β) may stimulate innate antiviral responses and are expected to have in vitro activity against SARS CoV-2, given the previously described activity demonstrated against MERS-CoV (EC50 175 IU/ml). However, toxicity includes severe cytopenias, hepatotoxicity (including fatality), neuropsychiatric events, and the risk of developing fatal or life-threatening ischemia or infection, especially when combined with Ribavirin are significant [16].

Remdesivir:

Remdesivir (GS-5734) is a new nucleoside analogue and has been recognized as a potential and promising antiviral medication against a wide range of RNA viruses, including SARS/ MERS-CoV [17]. Remdesivir was developed by Gilead Sciences, Inc., investigational mono phosphoramidate prodrug of an adenosine analogue, as a response to the Ebola outbreak in West Africa from 2014 to 2016. In its active triphosphate nucleoside form, Remdesivir acts as an RNA-chain terminator by binding to ribonucleic acid (RNA)-dependent RNA polymerase [18]. Remdesivir and IFN-beta antiviral activity was found to be superior to that of the Lopinavir /Ritonavir and IFN-beta combination against MERS-CoV [19]. At present, two randomized, controlled, double-blind clinical trials are enduring to evaluate the efficacy and safety of Remdesivir (200 mg loading dose on Day 1, followed by 100 mg i.v. once-daily maintenance dose for 9 days) in hospitalized patients with mild/moderate or severe COVID-19 respiratory disease. The results of these clinical trials may look forward to effective antiviral therapy for such an epidemic infectious disease [20]. Sheahan, *et al* [21] demonstrated that in a human airway epithelial cell model Remdesivir shows a wide therapeutic index. The drug also exhibits a high genetic resistance barrier in corona viruses, and has a long intracellular half-life that allows for once daily dosage [22].

Ironically, the adaptive clinical trial protocol originally claimed that Remdesivir is a drug that is metabolized as a CYP-3A4 substrate to its active form." This implies the existence of interactions between drugs and CYP3A4 substrate inhibitors, such as Ritonavir or Voriconazole. However, the protocol also claimed that although Remdesivir is a substratum for in vitro CYP2C8, CYP2D6, and CYP3A4, coadministration with inhibitors of these CYP isoforms is unlikely to significantly increase the levels of Remdesivir, as its metabolism is likely to be predominantly mediated by hydrolase. Unlike the former, the latter statement is substantiated by well-described molecule chemistry. Contact was made to the National Institute of Allergy and Infectious Diseases regarding this discrepancy, and this has been corrected in collaboration with Gilead. There is no reason to believe that any significant interactions between the inhibitors or inducers of Remdesivir and CYP3A4 are likely [23].

Emerging clinical evidence and available *in vitro* data indicate that Remdesivir is a promising agent for COVID-19 therapy. Clinical trial enrolment or reasonable use of Remdesivir for moderate-to - severe patients should be studied by the institutions.

Both prophylactic and therapeutic Remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology in a mouse model of SARS-CoV pathogenesis [21]. Remdesivir was used to treat the first case of COVID-19 infection in the United States: the clinical condition of the patient improved within one day of treatment with Remdesivir [24].

Neuraminidase Inhibitors:

Neuraminidase inhibitors are recommended for influenza management. Oseltamivir was also used in the management of 2019-nCoV; however, definite evidence of efficacy is not conclusive due to the lack of an appropriate control group in the studies [25]. A total of 35 patients received Oseltamivir (37.6 %) in a study of

possible MERS-CoV cases in Paris from 2013 to 2016. In patients positive for influenza virus (n = 25), 52 % (n = 13) received Oseltamivir and it was concluded that empirical Oseltamivir can be started in suspected MERS-CoV cases [26]. Many other studies have also evaluated Oseltamivir in MERS-CoV [27]. It is important to note that the use of Oseltamivir was not as targeted SARS-CoV-2 therapy, but was driven by a lack of knowledge of the causative pathogen at the time of treatment and a desire to empirically treat influenza [15]. Coronaviruses do not use neuraminidase, and therefore Oseltamivir does not inhibit enzymes. That will be true for Zanamivir, Peramiviror any other agents inhibiting neuraminidase. Similarly, neither an established mechanism nor *in vitro* data has indicated that Baloxavir displays activity against SARS-CoV-2 or other coronaviruses. Therefore, given the critical need for these agents in influenza management and the concern for Oseltamivir drug shortages, these agents should be avoided in patients with COVID-19 once influenza has been ruled out [28].

Protease Inhibitors:

SARS-CoV contains two types of protease, the CL-like protease, and the papain-like protease, which perform important functions in the life cycle of CoVs. Among protease inhibitors, Lopinavir was the most inhibitor and Saquinavir was the least powerful CoV protease inhibitor [29]. In molecular dynamic studies, flap closure was observed when these inhibitors were bound to SARS-CoV 3CL (pro) [30]. According to the current guidelines, Lopinavir + Ritonavir is the recommended protease inhibitor for 2019-nCoV treatment (weak recommendation) [31].

Lopinavir/Ritonavir:

Lopinavir is a human immunodeficiency virus (HIV)-1 protease inhibitor given in a fixed-dose combination with Ritonavir (LPV / r), a potent CYP3A4 inhibitor that "boosts" concentrations of Lopinavir. Lopinavir tends to block the main protease of SARS-CoV-1, inhibiting viral replication [32]. The convincing mortality discrepancy in SARS-CoV-1 and continued investigation in MERS-CoV led to the inclusion of LPV / r in the Chinese SARS-CoV-2 guidelines at a dose of 400 mg/100 mg (2 capsules / tablets) by mouth twice a day for no more than 10 days, although we know that there are no *in vitro* LPV/r data in SARS-CoV-2. For pediatric patients of weight 15 to 40 kg, the recommended dose in the United States is 10 mg/kg suspension by mouth twice daily [33].

Real-world data for treatment of COVID-19 with LPV/r are emerging. Young *et al*. [34] reported outcomes of the first 18 patients infected with SARS-CoV-2 in Singapore, 5 of whom received LPV/r monotherapy. Three patients had reduction in oxygen requirements after treatment initiation; 2 worsened with respiratory failure.

Two of 5 patients (40 %) reported clearance of viral shedding on medication, and 4 of 5 (80 %) encountered adverse events that precluded completion of the scheduled 14-day treatment course. With the available data, it is difficult to assess whether LPV / r has a role either as a monotherapy or in combination for the treatment of COVID-19. More importantly, it warrants comment that in the recent randomized controlled COVID-19 pneumonia trial, the median time from the onset of symptoms to the treatment was 13 days and, in the SARS-CoV-1 experience, therapy appeared to be effective if initiated early but not as rescue and/or rescue [35].

The combination of Lopinavir / Ritonavir with Ribavirin has been reported to reduce the risk of ARDS compared to Ribavirin alone [36]. Recently, the randomized clinical trial of Lopinavir / Ritonavir (400 mg/100 mg, twice daily for 14 days) in the treatment of COVID-19 by Cao, *et al*., showed that no beneficial effect was observed with severe COVID-19 in hospitalized adult patients. The side effects of treatment with Lopinavir/ Ritonavir include anorexia, nausea, abdominal discomfort, diarrhoea, or acute gastritis [37].

Umifenovir (Arbidol):

Arbidol is a small indole-derivative molecule and is approved for the prophylaxis and treatment of influenza and other respiratory viral infections [6]. It also showed inhibitory activity against other viruses, whether enveloped or not, responsible for emerging or globally prevalent infectious diseases such as hepatitis B and C [38]. Moreover, Arbidol has been reported to have antiviral activity against the pathogen of SARS, and the effect of Arbidol mesylate - a derivative of Arbidol, was almost five times higher than Arbidol in reducing the reproduction of SARS in cells *in vitro* [39]. Arbidol was believed to have been effective against 2019-nCoV *in vitro* [40]. A randomized multicenter-controlled clinical trial of Arbidol in patients with 2019-nCoV in China is in progress [41].

Chloroquine and Hydroxychloroquine:

Chloroquine, an antimalarial agent with anti-inflammatory and immune modulatory properties, has gained considerable attention as a possible therapeutic alternative for the management of COVID-19 [42]. It was found to be a potent inhibitor of SARS-CoV infection due to its inhibitory effect on ACE2 [43]. It has been demonstrated that 2019-nCoV penetrate the epithelial cells of oral mucosa through the critical receptor ACE2 [44], and Chloroquine can function at both entry and post-entry stages of 2019-nCoV infection. In early February, Wang,*et al*. [3] demonstrated potent Chloroquine *in vitro* activity against SARS-CoV-2 with an EC50 of 1.13 μM in Vero E6 cells at 48 h. These data were consistent with previous data for the inhibitory activity of chloroquine against SARS-CoV-1 and MERS-CoV in different cell lines, where EC50 values of 1 to 8.8 and 3.0 μM were shown, respectively [42]. These findings supported the clinical use of Chloroquine in numerous clinical trials in China during this outbreak at a dose of 500 mg by mouth twice daily. Recently, Wang et al. have shown that Chloroquine is highly effective in *in vitro* control of 2019nCoV infection and is suggested to be assessed in COVID-19-patients [18].

Additionally, interest has arisen in Hydroxychloroquine, a drug that differs from Chloroquine by a single hydroxyl group only. Historically, very few data were published evaluating the efficacy of Hydroxychloroquine against coronaviruses [46]. The investigators then conducted PBPK modelling to inform optimal dosing of Hydroxychloroquine. Various dosing regimens have been simulated but two are especially noteworthy. The first was a 1200 mg (divided 800 mg then 400 mg) oral charge dose on day 1, followed by 400 mg daily.

The second treatment was an 800 mg (400 mg twice) loading dose on day 1 followed by 200 mg twice daily. Such doses have been related to higher RLTEC values than Chloroquine. The authors concluded that these data support the lower dose plan because RLTEC values were significantly higher than those with the proven effective 500 mg Chloroquine regimen taken by mouth twice daily [47]. In 2006, Biot, *et al*., evaluated the comparative inhibitory activity of chloroquine and Hydroxychloroquine in Vero cells against SARS-CoV-1. The authors demonstrated that chloroquine had an approximately 5-fold increase in potency compared to hydroxychloroquine [46]. In COVID 19 treatment, Hydroxychloroquine sulfate 400 mg given twice daily for 1 day, followed by 200 mg twice daily for another 4 day is recommended [47].

The first result obtained from over 100 patients showed the apparent efficacy of chloroquine in terms of reduction of pneumonia exacerbation, duration of symptoms and delay of viral clearance, all without serious side effects [45].

Nitazoxanide:

In addition to coronaviruses, Nitazoxanide displays wide-spectrum antiviral activity *in vitro* against influenza, respiratory syncytial viruses, Parainfluenza, rotavirus, and Norovirus among others [48]. Nitazoxanide is being investigated for influenza management and other acute respiratory infections due to the wide-spectrum antiviral activity. Positive results were demonstrated in an outpatient influenza management phase 2b/3 study in which a dose of 600 mg of Nitazoxanide BID per mouth was associated with an improvement of ~1 day in symptom resolution compared to placebo (P = 0.008) [49]. Even when Nitazoxanide's *in-vitro* activity against SARS-CoV-2 is encouraging, more data is clearly needed to determine its role in COVID-19 management.

Adjunctive Therapies Used In COVID 19 Treatments:

Corticosteroids:

Corticosteroids have been widely used to treat SERS-CoV and MERS-CoV, and are also used to manage the current 2019-nCoV epidemic. However, the WHO's interim guidelines prohibit the use of routine corticosteroids unless indicated for other clinical grounds [50]. Corticosteroid use is reported to be associated with delayed viral RNA clearance (both in the case of SERS-CoV and MERS-CoV) and other steroid-related complications such as psychosis [12].

Interferones:

Interferon (IFNs) are antivirals of broad spectrum, primarily used in hepatitis B treatment. In SARS-CoV patients, the benefit was seen on the IFN-α + high-dose corticosteroid group compared to ribavirin or interferon (IFN) alone [51]. For the 2019-nCoV treatment, IFN-α (5 million U BID Inhalation) is recommended along with the combination of Lopinavir + Ritonavir [31].

Immunoglobulin:

In the case of critically ill SARS, which has signs of worsening, more immunomodulation escalation is suggested and intravenous (i.v.) immunoglobulin may be

considered [52]. Patients with inadequate response to initial clinical therapy may benefit from i.v. Immunoglobulin [53].

Thymosin alpha-1:

Thymosin alpha-1 is a Thymicpeptide hormone with significant advantages in restoring the host immune system's homeostasis [54]. Low lymphocyte counts have been reported to be associated with weak septic patient prognoses.

The use of Thymosin alpha-1 therapy in combination with conventional medical therapies has been effective in improving clinical outcomes and reducing mortality in severe sepsis [55]. Thus, although there is no clinical evidence showing the beneficial effects of Thymosin alpha-1 in COVID-2019, it has been recommended that some patients use it to enhance cell immunity for viral resistance.

Cyclosporine A:

Because of its immunosuppressive effect Cyclosporine A is widely used in transplantation and autoimmune disorders. Cyclophilin A as a key member of Immunophilins is the cellular receptor for cyclosporine A [56]. Cyclosporine A inhibition of Cyclophilins could block the replication of coronavirus, including SARS-CoV [57].

Therefore, non-immunosuppressive Cyclosporine A derivatives could be used as broad-range CoV inhibitors against emerging viruses such as 2019-nCoV, which still need to be confirmed by future clinical studies.

Antibacterial therapy:

Patients with pneumonia, especially those in serious condition, can experience co-infection or cross-infection of bacterial pathogens, such as *staphylococcus aureus*, during hospital medical care. It is essential to test the kinetics of procalcitonin (PCT) and C-reaction protein (CRP) in COVID-19 patients for timely diagnosis and intervention of bacterial infection, given the high incidence of bacterial infection in critically ill patients with COVID-19.

According to the recent 2019 ATS / IDSA clinical practice guidelines, in addition to antiviral treatment for patients with viral pneumonia, clinicians should empirically treat patients with severe diseases (extensive pneumonia, respiratory failure, hypotension, and fever) or deteriorate after initial improvement, or fail to improve after 3 to 5 days of antiviral treatment with antibacterial therapy [58].

CHINESE TRADITIONAL MEDICINE:

In 2003, traditional Chinese medicine was used for the prevention and treatment of SARS. In 2009, during the H1N1 influenza pandemic, China's Traditional Chinese Medicine issued a traditional Chinese medicine prevention programme, which included several Chinese herbal medicine formulas to prevent infection of adults and children [59]. ShuFengJieDu capsules and Lianhuaqingwen capsules also played a role in the prevention and treatment of new respiratory infectious diagnoses [60].

Some studies have reported that Yupingfeng powder has antiviral, anti-inflammatory, and immunoregulatory effects [61]. A large-scale, randomized, multicenter trial found that Yinqiao powder plus another heat-clearing combination could minimize fever resolution time in patients with the H1N1 influenza virus infection [62].

However, clinical trials need to further confirm the effectiveness and safety of these traditional Chinese medicinal formulae in COVID-19.

AN INSIGHT INTO AYURVEDIC TREATMENT MODALITIES:

At a generic level, key criteria for choosing suggested Ayurvedic medicines have been safety and potential efficacy, wide-spectrum applicability, ease of availability, long-term clinical experience, ease of administration, and affordability as far as possible [63]. Ayurveda and Yoga as an add-on therapy can support COVID-19 patients by improving the quality of standard care. For the purpose of Ayurveda interventions during COVID-19 pandemic, people can be categorized into four distinct categories [64].

Unexposed asymptomatic group:

This group will include people who currently have no associated symptoms and comorbidities [65].

Preventive interventions can include both pharmacological and non-pharmacological strategies in this group. Healthy lifestyles, adequate physical activity, sufficient sleep, care for retainable and non-retainable urges, sadvritta, and the prevention and isolation from infected persons are vital among the non-pharmacological interventions [66]. Fumigation of homes, shelters and living spaces by Ayurvedic herbs such as garlic (*Allium sativum*) peel, turmeric (*Curcuma longa*) powder, carom seeds or Ajwain seeds (*Trachyspermum ammi*) and Loban (resin of *Styrax benzoin* and Boswellia species) may also be a useful disinfection strategy [67]. Additionally, community-based Swarna Prashana [68] and

mass prophylaxis by rasayana [69] may also be a useful disinfection strategy. Brahma Rasayana, Chyavanprasha or Amrit Bhallataka are included in Rasayana [70]. Rasayana acts as an antioxidant, anti-stress, anti-inflammatory, anti-microbial, adjuvant vaccine and confer immunity to disease [71]. Furthermore, according to Ayurveda classics, rasayana therapy [72], together with physical and social distance from infected persons [73], constitutes a core strategy for overcoming epidemic and infectious diseases.

Exposed asymptomatic (Quarantined):

This group consists of people who have no apparent symptoms but are at risk because of history of contact. They do need to be carefully quarantined. For this group, specific prophylaxis may include Sanjeevanivati [74] and Chitrakadivati and combination of Guduchi (*Tinospora cordifolia*), Shunthi (*Zingiber officinale*), and Haridra (*Curcuma longa*). This choice of medicines aims to maintain both agni and aampachana in order to prevent the progression of pathogenesis in its initial stage of sanchayaprakopa-prasara [75]. A combination of Ayurvedic herbs such as *Tinospora cordifolia*, *Zingiber officinale*, *Curcuma longa*, *Ocimum sanctum*, *Glycyrrhiza glabra*, *Adhatoda vasica*, *Andrographis paniculata*, *Swertia chirata*, *Moringa oleifera*, Triphala and Trikatu may also be given for this group [76].

With mild COVID-19 symptoms:

This category relates to people who have been found positive for SARS CoV-2 and who have mild symptoms of URTI. They need to be carefully isolated and monitored for any disease progression, along with giving adequate therapy to evict the symptoms and balancing the vitiated doshas to control the progression of disease. Formulations such as Lakshmi Vilas Rasa [77], Pippali Rasayana [73], Sanjeevani Vati [78], Chitrakadi Vati, Gojihvaadi Kashaya, Vyaghri Haritaki, Kantakaari Avaleha, Dasha Mul Kwath, Sitopaladi [79], Talishadi and Yashtimadhu are perhaps the most appropriate drugs to be used in an integrative model at this stage.

With moderate to severe COVID-19 symptoms:

This category may be the population where there are already moderate to severe symptoms and patients also belong to high risk groups [79]. Suggested formulations here may include Pippali Rasayana, Laghu Vasant Malati, Sanjeevani Vati, Tribhuvankeerti Rasa [80], Brihata Vata, Chintamni Rasa, Mrityunjaya Rasa, and Siddha Makardhvaja Rasa.

Ayurveda practitioners would need training in screening the people for associated risk factors, along with the above plan. They should also be equipped with modern equipment for personal protection and access to the diagnostic facilities. Good networking between AYUSH health authorities and local health authorities will help in the current crisis to make effective use of human capital in the AYUSH community [81].

If adopted, this action plan has tremendous potential to give learning and inventive insights. So it is crucial to have proper documentation. It is therefore suggested that a proper documentation on each case of key variables which are important should be done. Such variables should include age, gender, symptoms, geography , history of touch, Ayurvedic diagnosis including roga and rogibala test, symptom improvement or worsening, dosage-based Ayurvedic medicine(s), final outcome of treatment, referral to secondary / tertiary care, managed, cured symptoms, and, if any, mortality. A follow-up advice should also be reported after discharge or stoppage of medications [82]. The selection of specific therapeutic agents and practices of Ayurveda is based on certain individual genetic characteristics known as types of Dosha Prakriti (Vata, Pitta, and Kapha) [83]. In our opinion, several general measures described below may be useful in reducing the risk of SARS-COV-2 infection and in complementing therapeutic management as an add-on treatment.

The eyes, nose, and mouth are the main droplet entry portals that hold the SARS-COV-2. The virus gains entry to the throat area and stays for several hours until the final attack in the lungs. The virus fatty acid coat adheres to the moist mucosal layers, which by binding to specific cell receptors helps it gain entry into the cells [84]. Ayurveda classics mention several interventions that are likely to target these entry portals. This may help strengthen the innate immunological response of the mucus membranes and may thus prevent the transmission of the virus to the lungs. In mild cases, the general measures for respiratory diseases described in ayurvedictexts [85] such as hot water consumption, hot food and herbal decoctions, gargling with medicated water, inhalation of steam, and local applications may be helpful for symptomatic relief.

Medicated water:

Drinking warm or hot water is a popular home remedy for many illnesses. This is also recommended by Ayurveda as a measure to improve the digestion of Ama,

a proinflammatory result of damaged metabolic disorders. Several spices which are popularly used in the kitchen are added to the boiling water as single or multiple agents and consumed throughout the day as medicines. These spices include dry ginger (*Zingiber officinale*), yashtimadhu (*Glycyrrhiza glabra*), and rhizomes of nut-grass (*Cyperus rotundus*), khus (Vetiveriazizanioides) and roots of Indian sarsaparilla (*Hemisdesmus indicus*), coriander (*Coriandrum sativum*) and fennel (*Cuminum cyminum*) leaves, and cinnamon (*Cinnamomum verum*) and catechu (*Acacia catechu*) barks [86].

Mouth rinse and gargle:

Warm liquids and oils are used for thorough cleaning of the mouth and throat as gargles (gandusha) or mouth rinses (kavala). This may also have a systemic effect [87]. Oils or oily decoctions purify the oral cavity, pharynx, and tonsillary region and are likely to cover the mucosa as a biofilm and cause additional immunomodulatory, antioxidant, and antimicrobial benefits [88]. Turmeric (*Curcuma longa*) rhizome, yashtimadhu or liquorice (*Glycyrrhiza glabra*), neem (*Azadiracta indica*) and catechu (*Acacia arabica*) barks, and natural salt may be used to prepare medicated water / solutions for gargles / mouth rinse [89]. Yoga texts recommend cleaning of nasal passage with salt water (Jalaneti) [90]. Salt water efficacy in upper respiratory infections has been reported in randomized controlled trials (RCTs), even though more conclusive evidence is needed [91].

Nasal oil application:

Ayurveda recommends the application of medicated oils made from butter oil (Ghee) and vegetable oils like sesame or coconut to the nostrils. This can prevent pathogen entry to the respiratory tract. This method, known as nasya, is well defined in Ayurveda [92]. Traditional Chinese Medicine researchers have also suggested the application of nasal oil to avoid infection with SARS-COV-2 [93].

Steam inhalation:

Steam inhalation and hot fomentation (with aromatic oils such as menthol) ensures satisfactory clinical relief in nasal and throat congestion, bronchoconstriction, headache, and sinusitis [94].

Yoga for Mental Health:

Poor mental health conditions, including stress and depression, are known to increase the risk of acute respiratory infections [95]. Increasing numbers of COVID-19 cases and deaths may increase stress and anxiety, while loneliness and depressive feelings are likely due to compulsory measures of social distance. Mind consideration is yet another distinction in both Ayurveda and Yoga.

Several mental health steps are discussed including pranayama and meditation. Pranayama is known to improve the function of the lung [96]. Yoga including meditation may be an easy and effective home-based activity for COVID-19 prevention and post-recovery management.

Modern technologies:

Inventions of modern technologies can play a major helping hand in tracking, diagnosing, treating and taking care of COVID19 patients. Artificial intelligence is a striking invention in the medical field. BlueDot is an Artificial Intelligence that helps detect COVID positive patients from those with communicable diseases. Other Artificial Intelligence's like Arogyasetu, Health Map all played a wonderful role during the pandemic period. Many Artificial Intelligence make quick and accurate diagnosis during X- ray and CT scan and help reduce the speed of spread of the disease [97]. Various forms of Artificial Intelligence systems, such as deep learning and Handcraft engineered features take little time and reduce the manual steps in providing detailed results faster and radio diagnosis and also help to determine between cancerous and noncancerous cells.GPS tracking has also proved to be useful for tracking home quarantined peoples [97].

CONCLUSION:

The new COVID 19 virus outbreak has challenged the country's face of medical, financial, and public health. There is no specific antiviral medication or vaccine used to treat this pandemic. The most important limitation of current CoV research is the lack of high-quality evidence (especially randomized controlled trials). Whilst still research is under way to improve COVID-19 prevention, treatment, and control. Interventions, including intense contact monitoring accompanied by quarantine and isolation, can effectively minimize COVID-19 spread, with the impact of restrictions on travel. Wearing masks, washing hands and disinfecting surfaces can reduce the risk of infection.

More quality efficient research is required in short time towards the study of SARS-CoV-2 in suitable animal models for analyzing replication, transmission, and pathogenesis.

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