Review Article:
Chemoprophylatic, Ayurvedic, Homeopathic Approaches for COVID-19 Prophylaxis

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ABSTRACT

The world is grappling for US FDA-approved therapies for Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). It is the virus that has caused Coronavirus Disease 2019 (COVID-19). Several pharmacological drugs are under various phases of clinical trials, and their current clinical use is primarily based on the in vitro activity against SARS-CoV-2 or related coronaviruses. While the efficacy of drug therapies is yet to be established, and the efficacy of the vaccine for COVID-19 is to be accomplished, we need to focus on prophylactic measures. The current article describes the chemoprophylactic, Ayurvedic, homeopathic, and Unani prophylactic approaches for combating COVID-19 based on the guidelines issued by the Ministry of AYUSH, India. The article is based on the guidelines issued by the Ministry of AYUSH, India. The proposed approaches have been supported by scientific evidence. The article also provides an outlook on the global scenario of herbal practices. In the absence of effective treatment, efforts to control the COVID-19 pandemic heavily rely on non-pharmaceutical interventions such as personal preventive measures. The alternative system of medicine offers prophylactic solutions that are simple and inexpensive. These simple measures will go a long way in tackling the pandemic.

1. Introduction

The spread

The SARS-CoV-2 virus, the cause of coronavirus disease 2019 (COVID-19), is asserted to be originated in bats that supposedly have evolved aggressive immune response to the virus. The immunity drives the virus to replicate fast to overcome the bat's immune system. As a result, the bats have transformed it into a reservoir of exceedingly transmissible virus [1]. On being transmitted to other mammals with an insufficiently strong immune system, the virus rapidly escalates into its new host. A wealth of evidence emphasized that SARS-CoV-2 got transmitted into humans through an intermediary host pangolin [2]. Other reports suggest direct transmission of the virus from bats to humans. The spread of SARS-CoV-2 among humans occurs via inhalation of droplets of water comprising the virus, expelled by an infected person through cough or sneeze. The trajectory of infected particles can range from 1 to 2 m.

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Infection overview

The virus borne droplets, when inhaled by non-infected humans, come into contact with the cells bordering the throat and larynx. These cell surfaces have abundant ACE-2 receptors, and the SARS-CoV-2 virus has a surface protein, Spike (S) protein that facilitates the entry into target cells. The viral access depends on the binding of the surface unit, S1, of the S protein to the ACE-2 receptor. Additionally, the entry requires S protein priming by a cellular protease that is primed to lock on the ACE-2 receptor and transmit its RNA into the cell. Once inside the cell, the viral RNA integrates with the replication process of the cell and produces multiple copies of the virus. The viral copies burst out of the cell, spreading the infection in the human body. As a result of infection, the antibodies are generated by the human immune system that targets the virus and, in most cases, halt its progression [3].

However, the virus can cause serious clinical complications when the infection spreads and progresses down the respiratory tract and infects the lungs with many ACE-2 receptors in the throat and larynx. Thus, the virus gets access to many cells that get destroyed, and the lungs become congested with damaged cells. In such cases, the patients require intensive care treatment [4]. In some instances, the patient's immune system gets extensively triggered, attracting antibodies to the lungs to combat the virus, causing inflammation. Occasionally, the process can get perpetuated. As a result, more neutralizing antibodies pour in, and the inflammation is aggravated. This phenomenon termed as cytokine storm is a potentially life-threatening event, particularly in the case of COVID-19 [5]. The reason why the cytokine storm occurs in some patients but not in others is not clear.

The patients recovering from COVID-19 infection have reported substantially high levels of neutralizing antibodies in their blood. These antibodies can coat the invading virus at specific points, thereby blocking its anchors to enter the cells [6]. Thus neutralizing antibodies can be both necessary and sufficient for rendering protection against viral infections, sometimes augmenting cellular immunity [7]. It has been evidenced that immune responses are intensified against COVID-19 in the infected people. The antibodies generated by the immune response can confer protection against relapse infections but is unlikely to protect for a lifetime. It is believed that the protection may last for a year or two after the COVID-19 infection [8]. Finally, an effective vaccine will be developed that will combat COVID-19.

WHO draft landscape on COVID-19 vaccine reports 10 candidate vaccines in clinical evaluation and 123 candidate vaccines in the preclinical evaluation stage. The platforms of the candidates in the clinical evaluation are non-replicating viral vector, RNA, inactivated virus, protein subunit, and DNA [9]. The vaccines are in various phases of clinical trials. This process inevitably is lengthy, and prophylaxis/prevention may be a practical temporary approach to tackle the pandemic. This research elaborates on the preventive aspects and prophylactic aspects of combating COVID-19. The latter describes the chemoprophylactic, Ayurvedic, homeopathic and Unani approaches primarily based on strengthening immunity. The article is based on the guidelines issued by the Ministry of AYUSH, India. The proposed approaches have been supported by scientific evidence. The article also provides an outlook on the global scenario of the herbal approaches.

Prevention of COVID-19

The key approaches to prevent the spread of COVID-19 are 1. Clean the hands frequently using an alcohol-based hand rub or soap and water; 2. Maintain a safe physical distance from the person who is coughing or sneezing; 3. Do not touch nose, eyes or mouth; 4. Cover nose and mouth with the bent elbow or tissue while coughing or sneezing; 5. In case of persistent cough, fever, compounded with difficulty in breathing, seek medical attention; and 6. Avoid unnecessary visits to hospitals allowing the healthcare systems to work efficiently, thereby protecting oneself and others. These measures are being promoted by national/local authorities, media, and WHO [8].

Prophylactic approaches

The function of the human immune system is an essential determinant in response to an infectious disease. Viral infections, in general, trigger oxidative stress and cause extensive damage to airway epithelial cells [9]. Growing evidence has identified nutrition, stress, and immunity as cofactors in susceptibility to infectious diseases and outcomes. In light of these facts, the mainstay approaches in managing corona viral infection, in the absence of any antiviral agent or vaccine, are good nutrition, supplemental care, and prevention of further progression of the disease [10, 11]. These objectives can be accomplished by the use of various prophylactic approaches detailed in the following.

Chemoprophylaxis

COVID-19 is a prevalent and contagious disease with substantial morbidity and mortality (mortality rate=2%-

3%), and no proven pharmacological treatment is currently available. Chloroquine and hydroxychloroquine drugs have been repurposed or repositioned clinically for combating the pandemic [12, 13]. The Indian Council of Medical Research (ICMR), under the sponsorship of the Ministry of Health and Family Welfare, New Delhi, India, has recommended a chemoprophylaxis regimen of hydroxychloroquine 400 mg twice on day 1, followed by a dose of 400 mg once a week for 5 to 7 weeks for asymptomatic health care staff engaged in treating the patients with suspected or confirmed COVID-19 [14]. The ICMR document states that "the use of hydroxychloroquine in prophylaxis is evidenced from treatment benefit observed clinically and is supported by the preclinical data." Although certain in vitro investigations have proved the antiviral effect(s) of hydroxychloroquine and chloroquine, there is no peer-reviewed research report that can affirm the prophylactic effect against SARS-CoV-2 infection for either of the two drugs.

Furthermore, only one study reported nasopharyngeal viral clearance, with no data for clinical improvement, when hydroxychloroquine was used to treat clinically-diagnosed cases of the infection [15]. This study hardly justifies the claimed widespread use of hydroxychloroquine for prophylaxis. The facts that cannot be ignored are 1. The drug is yet to be proven for clinical use; 2. The benefits not fully known; and 3. The risks are high, especially when it is to be used at this scale.

Many people who reside in the regions with a high risk of COVID-19 can be either healthy, SARS-CoV-2 negative, or healthy but with asymptomatic infection. In each category, chloroquine and hydroxychloroquine might prevent infection, thereby substantially reducing morbidity and mortality. The dose used may be the same as that used for the treatment of malaria. Research reports 50% inhibition of SARS-CoV replication at a chloroquine concentration of 8.8 μmol/L in Vero E6 cells. The IC50 value is substantially lower than the plasma concentration achieved in humans when the drug is used to treat malaria in a dose of 25 mg/kg for three consecutive days [16]. Thus it may be inferred that for long-term prophylaxis against SARS-CoV-2, lower doses of the antimalarial drug may be used.

Of the various mechanisms of action identified for chloroquine and hydroxychloroquine, the objective is to disrupt coronavirus replication in an early stage. It has also been documented that chloroquine affects the immune system activity by mediating an anti-inflammatory response, thereby reducing the potential damage due to the exaggerated inflammatory response [17]. Alternatively, the use of hydroxychloroquine is recommended, for which even greater efficacy has been reported in the in vitro studies on SARS-CoV-2 infected Vero E6 cells. The mechanism of hydroxychloroquine is similar to chloroquine, but the former is better tolerated and hence is a preferred drug for the treatment of malaria and autoimmune disorders. The immunomodulatory action of hydroxychloroquine may help control the cytokine storm in the late-phase in critically-ill SARS-CoV-2 infected patients. It must be noted that despite the widespread state-endorsed use, there is no evidence to support the clinical use of hydroxychloroquine in SARS-CoV-2 infection [13]. The prophylaxis rendered by the drug may last for the entire duration of the outbreak, specifically in countries in which malaria is not endemic, and there is no risk of adverse events associated with the resistance to this drug. But in countries where malaria is endemic, monitoring drug resistance against Plasmodium is essential. Moreover, it should be kept in mind that the safety of these immunomodulators in people at risk of a severe viral illness has never been evaluated.

Mahir Ozmen, a professor of surgery at Istinye University, School of Medicine in Istanbul, Turkey, suggested the use of chloroquine in combination with zinc and vitamins A and D. The clinical trial initiated on March 20, 2020, has a total of 80 participants that included professionals from healthcare sector mainly doctors, nurses, and their first degree relatives (father, mother, brother, sister, spouse, and children). The participants have been put on a single dose of 200 mg hydroxychloroquine (Plaquenil), repeated every 3 weeks plus vitamin C and zinc once a day. The main objective of the study was to include participants facing or treating SARS CoV-2 infected patients. The age, sex, comorbid diseases, smoking history, and body mass index were also recorded in the trial. The estimated study completion date is September 1, 2020 [18], and the results are awaited. Many clinical trials on chemoprophylaxis for COVID-19 have been registered in the US federal register. Table 1 presents a cross-section of prophylactic clinical trials registered at www.clinicaltrials.gov.

Ayurvedic prophylaxis

The Ministry of AYUSH, New Delhi, India, is equipped for providing an adequate response to the circumstances arising due to public health challenges. In the past, many interventions suggested by the AYUSH have been differently used in India for making an effective public response to such health challenges. In the current pandemic, AYUSH has provided guidelines for the prevention and prophylaxis of COVID-19 [20]. A notification

Table 1. A cross-section of clinical trials registered for chemoprophylaxis in the Federal Register [19]

Study	Intervention	Status	Location
Military COVID-19 hydroxychloroquine pre-exposure and post-exposure prophylaxis study	Drug: Hydroxychloroquine Dietary Supplement: Placebo	Not yet recruiting	Pentagon, Arlington, Virginia, United States
Chemoprophylaxis of SARS-CoV-2 infection in exposed healthcare workers	Drug: Hydroxychloroquine Drug: Placebo of hydroxychloroquine Drug: Ritonavir and lopinavir Drug: Placebo of LPV/r tablets	Recruiting	CHU d'Angers, France AP-HP - Hôpital, France CHU de Saint-Etienne, France
The PATCH Trial (Prevention And Treatment of COVID-19 with hydroxychloroquine)	Drug: Hydroxychloroquine Sulfate 400 mg twice a day Drug: Hydroxychloroquine sulfate 600 mg twice a day Drug: Hydroxychloroquine Sulfate 600 mg once a day Drug: Placebo oral tablet	Recruiting	University of Pennsylvania, Philadelphia, Pennsylvania, United States
Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	Lopinavir/ritonavir	Recruiting	Intermountain Medical Center, Murray, Utah, United States University of Utah, Salt Lake City, Utah, United States
Hydroxychloroquine in the prevention of COVID-19 infection in healthcare workers	Hydroxychloroquine	Enrolling by invitation	Baylor University Medical Center Dallas, Texas, United States
A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection	Drug: Hydroxychloroquine Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc	Not yet recruiting	ProgenaBiome, Ventura, California, United States
Pre-exposure prophylaxis with hydroxychloroquine for high-risk healthcare workers during the COVID-19 pandemic	Drug: Hydroxychloroquine Drug: Placebos	Recruiting	ISGlobal Barcelona, Spain

issued by the Ministry claims that these interventions from different AYUSH systems of medicine are supported with evidence for boosting immunity and mitigating the respiratory symptoms in similar diseases. The interventions are summarized below.

General measures

AYUSH recommends drinking warm water throughout the day, practicing Yogasana, Pranayama, and meditation for at least half an hour daily. The spices like Curcuma longa (Turmeric), Cuminum cyminum (Cumin), Coriandrum sativum (Coriander), and Allium sativum (Garlic) are recommended in cooking. All these herbs have antioxidant activity [21-24] and enhance immunity.

Ayurvedic immunity promoting measures

Ayurveda, being the science of life, propagates natural resources in maintaining health.

Traditional medicines to escalate immunity and resistance against disease are particularly relevant against the spread of the COVID-19 pandemic. The Ministry of AYUSH recommends some self-care approaches described herein: use of chyawanprash 10 g (1 tsp) in the morning; people with diabetes can use sugar-free chyawanprash. It is a potent antioxidant paste formulated via the synergistic blending of around 50 herbs, minerals, and spices, primarily used to promote health and immunity and prevent diseases [25]. It is an ancient Indian recipe (a polyherbal jam), prepared according to traditional Ayurvedic methods. It is widely used since ancient times, both as a medicine and as a health supplement for escalating longevity and immunity [26]. Chyawanprash is rich in vitamins, energy contents, protein, carbohydrates, dietary fiber, has low-fat content (zero percent cholesterol and no-trans fat), and appreciable levels of major and minor trace elements (mg/100g), such as Zn (3.1), Fe (21.1), Co (3.7), Mn (8.3), Ni (1.4), Cu (0.667), Pb (2.4), and carotenoids that act as micronutrients. It also is a rich source of several essential phytoconstituents, namely, alkaloids, flavonoids, antioxidants, saponins and, phenolic compounds. The rich nutritional composition and antioxidant biomolecules of chyawanprash act both alone and synergistically for immunomodulation [27, 28] and have the potential for prophylaxis against COVID-19.

AYUSH also recommends drinking herbal tea/decoction made from Ocimum sanctum (Basil), Cinnamon zeylanicum (Cinnamon), Piper nigrum (Black pepper), Zingiber officinale (Dry Ginger), and Vitis vinifera (Raisin) once or twice a day. The addition of jaggery (natural sugar) and or fresh lemon juice is recommended in herbal tea. Further, golden milk is advised for boosting

immunity; it can be prepared by boiling half teaspoonful of turmeric (Curcuma longa) powder in 150 mL hot milk and taking once or twice a day.

Ayurvedic procedures

AYUSH recommends certain procedures for body cleansing. These include the nasal application of coconut or sesame oil or clarified butter in both the nostrils (Pratimarsh Nasya) in the morning and evening, and oil pulling therapy: one tablespoon coconut or sesame oil to be taken in the mouth. Do not drink. Swish the oil in the mouth for 2 to 3 min and be spitted off, followed by mouth rinse with warm water. This practice is recommended to be done once or twice a day.

Remedies for dry cough / sore throat

Ayurveda recommends steam inhalation with fresh leaves of Mentha piperita (Mint) or Trachyspermum ammi (Caraway seeds) can be practiced once a day. Syzygium aromaticum (Clove) powder mixed with honey or jaggery can be taken 2-3 times a day in case of throat irritation or cough. These remedies generally treat sore throat and normal dry cough. Additionally, many more Ayurvedic prophylactic measures or the use of immunomodulatory drugs are recommended to strengthen the immune system through a healthy diet and lifestyle practices [29].

Patanjali Ayurved, an Indian consumer goods company that manufactures herbal and mineral products, has submitted a proposal to the Government of India for the "treatment and prevention" of COVID-19 using medicinal herbs along with hydroxychloroquine. The proposal stated that the phytochemicals in Withania somnifera (Indian ginseng), Tinospora cordifolia (Heart-leaved moonseed), and Ocimum tenuiflorum (holy basil) have the potential to fight COVID-19 [30]. The evidence to the claim is awaited.

Homeopathic prophylaxis

Homeopathic treatment is based on an atypical approach wherein similar symptoms of that particular disease are introduced. It is believed that this can automatically trigger the body's immune system by provoking it to fight against the illness and treat the patients [31]. Homeopathy has a successful history in the treatment and prevention of epidemics such as smallpox, cholera, diphtheria, malaria, yellow fever, and leptospirosis [32]. In January 2019, the AYUSH Ministry in India issued a recommendation for the prevention of coronavirus transmission. The Ministry recommended that homeopathic arsenicum album 30C was to be taken once per day for three days as a preventive measure [20].

Unani prophylaxis

Unani medicine is an alternative medicine system that originated in ancient Greece but is currently practiced primarily in India. It involves the use of dietary practices, herbal remedies, and alternative therapies that address mostly the prevention and treatment of disease.

According to Unani medicine practice, to maintain human health, a right balance of the bodily fluids (blood, phlegm, yellow bile, and black bile) known as "the four humors" is essential. Another key principle is that a disease is manifested due to an imbalance in air, earth, water, and fire: the four elements that constitute the human body. Besides, the medical system is partly based on the principle that the environmental conditions, including the quality of water and air, can significantly impact human health.

The Unani medicines or practices recommended for symptomatic management of COVID-19 infection are as follows 1. Sharbat Unnab: 10-20 mL twice a day; 2. Tiryaq Arba: 3-5 g twice a day; 3. Tiryaq Nazla: 5 g twice a day; 4. Khamira Marwareed: 3-5 g once a day; 5. massage on scalp and chest with Roghan Baboona/ Roghan Mom/ Kafoori Balm; 6. application of Roghan Banafsha gently in the nostrils; 7. Arq Ajeeb 4-8 drops in freshwater to be used four times a day; 8. In case of fever, 2 pills of Habb e Ikseer Bukhar with lukewarm water to be taken twice daily; 9. 10 mL Sharbat Nazla mixed in 100 mL of lukewarm water to be taken twice daily; and 10. 2 tablets of Qurs e Suaal to be chewed twice daily. The Unani system also recommends Arq (Juice) extracted from Unani drugs (Table 2) along with Sharbat Khaksi for the management of COVID-19 [20]. Sharbat Khakshi is a proprietary Ayurvedic preparation useful in measles and chickenpox [33].

Unani system of medicine also recommends a decoction of the following single Unani drugs listed in Table 3. Decoction is widely used in Chinese herbal medicine as well. Decoctions are liquid preparations that are usually administered orally, get absorbed quickly, and have potent action amongst all of the traditional types of preparation. The drawbacks of decoctions are as follows: they need considerable time for preparation, which is the primary obstacle in chronic diseases where many doses are required; they do not always taste pleasant; and they are not easy to transport or store [34].

Table 2. Unani drugs to be taken as juice along with Sharbat Khaksi

Unani Drug	Common Name	Botanical Name
Chiraita	Indian Gentian	Swertia chirata Karst
Kasni	Common chicory	Cichorium intybus Linn.
Afsanteen	Common sagewort	Artemisia absinthium Linn.
Nankhawa	Caraway	Trachyspermum ammi Sprague
Gaozaban	Borage	Borage officinalis Linn.
Neem Bark	Margosa	Azadirachta indica A. Juss.
Saad Koofi	Cypriol	Cyperus scariosus R. Br.

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Table 3. Decoction of drugs recommended by AYUSH

Unani Drug	Common Name	Botanical Name	Quantity/100 mL
Behidana	Quince	Cydonia oblonga	3 g
Unnab	Jujubi	Zizyphus jujube Linn.	7 nos
Sapistan	Assyrian plum	Cordia myxa Linn.	7 nos
Darchini	Cinnamon	Cinnamomum zeylanicum	3 g
Banafsha	Sweet violet	Viola odorata Linn.	5 g
Berg-e-Gaozabaan	Borage	Borago officinalis Linn.	7 g

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Global scenario of herbal therapy

In comprehensive research on traditional medicine guidelines, Ang et al. (2020) searched 7 data sources up to March 6, 2020, and discovered a total of 28 traditional medicine guidelines that suggested treatment approaches for COVID-19. Out of these, 26 were state-issued Chinese guidelines, and 2 were of Korean government guidelines. According to the report, the Japanese government did not officially issue any traditional medicine guidelines on COVID-19. Instead, they have adopted a translated version of the national guidelines issued by the National Health Commission, China. The research data analysis revealed 8 pattern identifications and 23 herbal formulae for the mild stage, 11 pattern identifications and 31 herbal recipes for the moderate stage, 8 pattern identifications and 21 herbal recipes for the severe stage, and 6 pattern identifications and 23 herbal formulae for the recovery stage in accordance to the Chinese guidelines. In the Korean guidelines, there were 4 pattern identifications and 15 herbal recipes for the mild stage, 3 pattern identifications and 3 herbal formulae for the severe stage, and 2 pattern identifications and 2 herbal formulae for the recovery stage.

The frequency analysis of herb usage revealed that both Ephedrae herba and semen armeniacae amarum were used in the highest frequency to treat the mild, moderate, and severe stages. The herbs gypsum fibrosum and lepidii seu descurainiae semen were also frequently used in the moderate and severe stages. Besides, Agastachis herba, Forsythiae Fructus, Atractylodis rhizoma, and Scutellariae radix were used in both the mild and moderate stages. Notably, radix glycyrrhizae afforded the highest usage frequency in all four stages. It was also the herb with the highest frequency of usage in total in Chinese traditional medicine.

2. Conclusion

Many clinical trials are underway to find a definite treatment and a vaccine for the prophylaxis of COVID-19. Chloroquine phosphate and hydroxychloroquine have repositioned as drugs of therapy for the current pandemic. Amidst all the COVID-19 clutter across the

globe, the clinical trials will move at their own pace, and hence prophylaxis can be seen as an interim measure. The literature on alternative medicine provides abundant, inexpensive approaches to combat the COVID-19 pandemic. Traditional approaches may be seen as supplemental therapy as immunity boosters to fight the disease. Aggressive research efforts will definitely pave the way for a better future.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors report no potential conflict of interest.

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