Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Evidence-based traditional Siddha formulations for prophylaxis and management of respiratory symptoms in COVID-19 pandemic-a review

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ABSTRACT

The recent outbreak of COVID-19 is attributed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This viral disease is rapidly spreading across the globe, including India. The mainstay in managing the disease is supportive care, nutrition, and preventing further progression in the absence of proven antiviral drugs. Currently two vaccines Covishield and Covaxin are administered in India. Long-term plans of developing most reliable mRNA-based vaccines are also underway for the future method of prophylaxis. The Siddha system of medicine's holistic approach emphasizes lifestyle modification, prophylactic interventions, and dietary management to boost the host immunity and treatment with herbal medicines and higher-order medicines as the case may be. In this review, a brief outline of the disease COVID-19, Coronavirus, evidence-based traditional Siddha interventions for respiratory ailments and immune boosters highlighting the relevant published research on individual herbs are dealt, which pave way for further research on drug repurposing for COVID-19. Historical evidence on the prevention and treatment of infections especially antivirals in Siddha classics is studied.

1. Introduction

The recent outbreak of COVID-19, primarily in Wuhan, China, resulted in an international concern and was declared a public health emergency. Pneumonia associated with COVID-19 has raised global concern. The lack of proven antiviral drugs, vaccines, and asymptomatic carriers has made long-standing public health intervention procedures ineffective in controlling the disease's spread (Sun et al., 2020). The novel coronavirus 2019, also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is caused by the infection of SARS-CoV-2 that prevailed from Wuhan. Currently, it is almost more than 200 countries. Primarily, the efforts were made to focus more on clinical courses, identify and treat critically ill cases, and symptomatically treat the sick as the spread of coronavirus progresses with outbursts of pandemic influenza, Middle East respiratory syndrome (MERS), and other symptoms. This had necessitated understanding the public health activities to eradicate the incidence, prevalence, and spread of the novel Coronavirus and depict the possible effects. The epidemiology is solemnly dependent on the persons infected, their transmissibility, and their severity (Lipsitch et al., 2020).

1.1. COVID-19 pandemic

WHO termed the disease COVID-19, acronym for "coronavirus disease 2019" on February 11th, 2020, by adopting the norms for specifying WHO's human infectious diseases. This practice of naming contagious diseases in humans was established in consultation and association with the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO). Egypt was the second country in the WHO EMRO region to record the first confirmed

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case on February 15th, 2020 (Rothan and Byrareddy, 2020). Many countries worldwide have now contained the spread of the disease by strictly following the preventive measures. India combated the first wave of Covid 19 effectively. Currently India is witnessing the second wave of COVID 19 with very colossal death toll. Also experts have commented that this rapid surge shows the fast transmission of virus from person to person during the second wave in India. WHO has updated the risk assessment of the danger of spread and risk of effect on COVID-19 to be inflated at the global level. From February 20th, 2020 to February 28th, 2020 nearly 25 new countries have reported COVID-19 prevalence. The global figure of registered COVID-19 patients has raised to 3,435,894 cases by May 04th, 2020 causing 239,604 deaths by affecting 212 countries and territories. The spread of this novel coronavirus has been brought under control in China (Salzberger et al., 2020). The European territory becomes the epicenter for a pandemic on March 14th, 2020 with more reported cases and death than the rest of the world combined other than China (Grasselli et al., 2020; Onder et al., 2020).

1.2. Coronavirus: an overview of the virus

Coronaviruses are single-strand RNA viruses causing enzootic diseases (Schoeman and Fielding, 2019), categorized into four subgroups as alpha, Beta, Gamma, and Delta. Human coronavirus 229E (HCoV-229E), Human coronavirus NL63 (HCoV-NL63), Transmissible gastroenteritis coronavirus (TGEV), Canine coronavirus (CCoV), Porcine respiratory coronavirus (PRCoV), Feline coronavirus (FeCoV), Porcine epidemic diarrhoea coronavirus (PEDV) are categorized under α-CoVs. Human coronavirus 4408 (HCoV-4408), Human coronavirus OC43 (HCoV-OC43), Human coronavirus HKU1 (HCoV-HKU1), Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle Eastern respiratory syndrome coronavirus (MERS-CoV), Bat coronavirus (BCoV), Porcine hemagglutinating encephalomyelitis virus (HEV), Murine Hepatitis Virus (MHV) are further characterized under β-CoVs. γ-CoVs include Avian infectious bronchitis virus (IBV) and Turkey coronavirus (TCoV) (Jimenez-Guardeño et al., 2014; Cui et al., 2019). So far, there are six Coronaviruses infecting humans, and among them, only the following viruses HCoV-NL63, HCoV-229E, HKU1, and HCoV-OC43 have been infected humans during the past two decades.

In late 2019, there were several outbreaks of novel Pneumonia in a Seafood market in Wuhan, Hubei province, China, caused by a novel beta coronavirus-Wuhan coronavirus sharing 79.5% of the genome similarity with SARS-CoV, which caused 2002–2003 pandemic and renamed as SARS-CoV-2 by International committee on taxonomy of viruses (Firas et al., 2020). Later by January 30th, 2020, WHO declared the COVID-19 as the sixth major international public health emergency. Human coronaviruses are transmitted from animals, either rodents or bats, and this particular SARS-CoV-2 has reportedly been spread from pangolins in China (Cyranoski, 2020). These viruses are enveloped with a lipid layer containing spikes-like structure resembling crown and hence the name Coronavirus (Crown in Latin - Corona) (Fig. 1). These spikes include several unique diversified surfaces receptor-binding domain (RBD), which bind with the angiotensin-converting enzyme-2 (ACE-2) receptor present in lungs, heart, gastrointestinal tract, and kidneys which form (Ksiazek et al., 2003) the viral admission into the host cell (Firas et al., 2020).

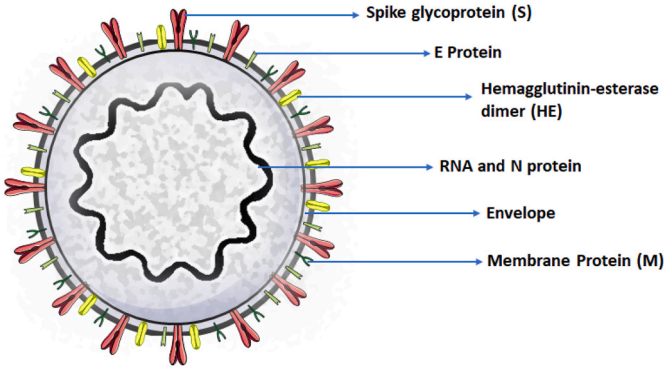

Fig. 1. Structure of coronavirus (COVID-19).

After the viral entry, the SARS-CoV-2 fix to the ACE-2 receptors in the type II pneumocytes found in the lungs. This attachment triggers a cascade of inflammatory processes in the lower respiratory system. Further, it activates the spike protein through a process of type 2 transmembrane protease TMPRSS-2 which further leads to the cleavage of ACE 2 (Fig. 2) (Kuba et al., 2005; Glowacka et al., 2011; Heurich et al., 2014). This route of cellular infection triggers the immune response of the host and activates the inflammatory cascade through the initiation of antigen-presenting cells (APC), which performs two significant functions viz., exposing the antigen to CD_4^+- Th1 cells and liberating IL-12 to stimulate the T helper cell further and followed by stimulation of CD_8^+-Tk cells. This, in turn, targets any cells with the extraneous antigen, followed by B-cells' stimulation to yield antigen-specific antibodies by activating Th1 cells (Firas et al., 2020). The immunocompromised host becomes more susceptible to this virus and increases the mortality rate. WHO reported the transmission rate of this virus *i.e.*, R0, to be between 1.4 and 2.5 and the incubation period after the viral entry into the host organism ranging from 2 to 14 days, making them more vulnerable to transmit through respiratory droplets than airborne transmission. Asymptomatic transmission made them to isolate the infected patients and cure them effectively. Also, age-related risks and pre-existing diseases increase the fatality rate (Firas et al., 2020).

In the current scenario, the management of novel coronavirus infection is focused on supportive care and testing the prevailing anti-corona viral drug's efficacy. Antiviral drugs used during the past epidemics of beta coronavirus, such as interferon, darunavir, ribavirin, and lopinavir, are currently being evaluated for their potential through in vitro tests (Chu et al., 2004). Initially, Adenosine analog, Remdesivir, which was earlier used against RNA viruses like SARS, MERS, and Ebola treatment, was used to treat the SARS-CoV-2 infection (Sheahan et al., 2017). Also, Camostat mesylate, Chloroquine, and Hydroxy Chloroquine are being used as potent drugs to fight the SARS-CoV-2. Chloroquine and Hydroxy Chloroquine block the viral cell fusion and inhibit RBD glycosylation and cellular receptors of ACE-2, limiting the interaction and inhibiting the viral attachment to the host cells (Fig. 2) (Firas et al., 2020). A long-term plan of developing most effective mRNA-based vaccines is underway for the future method of prophylaxis. The recent finding focuses on targeting ACE-2 receptor interaction for which the convalescent sera are also used to treat the disease (Firas et al., 2020).

2. Current COVID treatment in India and why there is a need for alternative therapy

The antimalarial drug hydroxychloroquine has been authorized by The Indian Council of Medical Research (ICMR) as a prophylactic drug for frontline COVID warriors, including those in close contact with positive cases suspected COVID-19 patients and the family members of confirmed cases. The medication is prescribed at a dose of 400 mg B. D on day 1, then 400 mg O. D for a week after that. The WHO initiated the "solidarity trial" in many countries to compare the medicines' effectiveness, such as Remdesivir, Lopinavir/Ritonavir with interferon beta, Lopinavir/Ritonavir, and Hydroxychloroquine against the novel coronavirus infection. FDA has not approved any drugs for COVID-19 in India right now. The patients are treated symptomatically. Of late, the US FDA has approved plasma therapy. Plasma therapy is recommended for the treatment of critical or life-threatening COVID-19 infections (www.who.int/emergencies/diseases/novel-coronavirus-2019). Due to the side effects it cause, antiviral therapy cannot be continued in the long run. The prevailing treatment for viral infections is not very

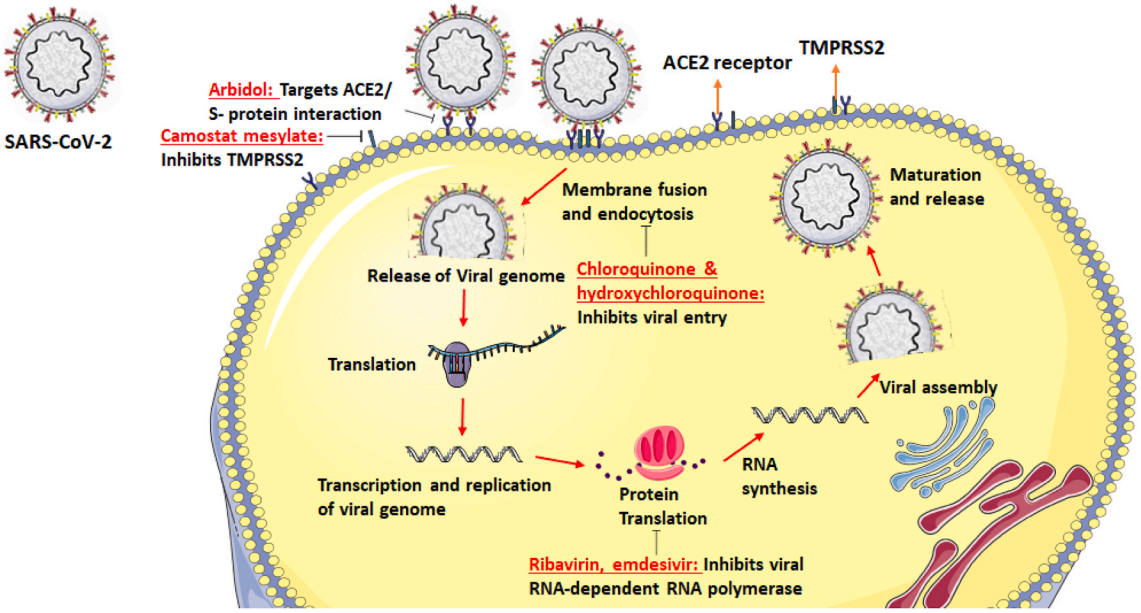

Fig. 2. SARS-CoV-2 Pathogenesis and different potent Drug targets.

effective and satisfactory all the time and is also not well-tolerated always (De Clercq, 2002). In a densely populated country like India, the COVID-19 outbreak creates a significant threat to the public. India is taking all necessary actions to contain the spread of the novel coronavirus. Currently, the prevalence in India is on the verge of Stage 2 to Stage 3.

In India, the morbidity profile, deficiency of infrastructures in health care, etc., have made COVID-19 a severe challenge. Around a 50 million people suffer from Diabetes mellitus, and approximately a 54 million are diagnosed with Cardio Vascular Diseases. Additionally, Pulmonary tuberculosis affected population is more in the country. These diseases challenge the immune system and might cause hindrance to the treatment. Hence, traditional medicine resources can be widely used for handling the current crisis. There are 291 Siddha hospitals, 848 Siddha dispensaries, 9125 Registered Siddha practitioners, and 5685 Institutional Qualified Registered Practitioners in India to fight against the COVID-19 pandemic (https://main.ayush.gov.in/https://health.ncog.gov.in/).

According to the Ministry of Health and Family Welfare, Government of India COVID-19 dashboard, the statistics of COVID-19 infected cases as of May 8th, 2020 is projected as **37916** active cases, **1886** death due to coronavirus infection and **16539** were cure/discharged, and one patient has migrated. The Central Government has given heeds to the Advisory from the Ministry of AYUSH, Government of India, and promoting the AYUSH systems though there is a lack of research evidence at present. The AYUSH Ministry has been propagating the AYUSH medicines for boosting immunity. The Government of Kerala started using Ayurvedic medicines along with the routine protocol. With a vision, in Tamil Nadu, the Government issued a G.O. (Ms). No.201 for implementing a unique program, "AAROKYAM" with AYUSH interventions for COVID -19 patients wherein the Siddha formulations *Kabasura kudineer/Nilavembu kudineer* is recommended for immune enhancement and *Ammukara chooranam, Nellikai lehyam* in the convalescence period. In addition to this, as per the Ministry of AYUSH, Corona Advisory– D.O. No. S. 16030/18/2019– NAM; dated: March 06th, 2020 *Visha sura kudineer,* and *Kaba sura kudineer* have been mentioned in *add ons* to conventional care.

2.1. Role of Siddha

The Siddha medical system is a comprehensive traditional medicinal system with its origin in India's southern part. It has now started spreading its roots across the globe. The immune-boosting food and medicines are available in plenty in the Siddha system of medicine.

Though Siddha medicine does not deal with coronavirus directly, there is a mention about the infectious diseases in Siddha classics Guru naadi, which clearly scraps out the etiology of diseases. The symptoms of COVID-19 are congruent with *Kapha suram/Iya suram* mentioned by the sage *Yugi* in his textbook *Yugi Vaidhya Chindhamani* (Mudhaliyar, 2004). According to Siddha's theory, *Vali* or *vatham* (Aiery), *Azhal* or *pitham* (Fiery), *Iyam* or *kapham* (Watery/cool) are the three humors which are the life constituents of the human body. Predominantly *Vatham* is found between the perineum and umbilicus, *pitham* is present from the umbilicus to the chest and predominant *Kapham* exists from the chest to the top of the head. The ratio between the three humors Vali, Azhal, and Iyam exists in the proportion of 4:2:1 in a healthy individual. Any imbalance in this ratio will result in disease (Anaivarai and Anandhan, 2009).

2.2. Siddha way of prevention

Prevention is better than cure is a Siddha doctrine. "Food is medicine, and medicine is food" is the prime principle of the Siddha system of medicine (Anaivarai and Anandhan, 2009). This reveals the importance given to a nutritious diet in boosting immunity and disease prevention. Rules for healthy living are stated in Siddha literature, which will prevent the disease entry when adhered. According to the Siddha classical textbook, Pathartha Guna Chindhamani, one should consume boiled water, diluted buttermilk, and melted ghee. Additionally, Over-indulgence in sex should be avoided. Drinking cow's milk, bathing in hot water following oleation should be practiced for a healthy living (Anaivarai and Anandhan, 2005).

2.3. Siddha philosophy

Siddha's treatment is personalized based on the *naadi* (pulse) and *thegam* (Body constitution) of an individual. The disease diagnosis is through *envagai thervu* (Eight folds of diagnosis) ie, *Naa* (Tongue), *niram* (Complexion), *mozhi* (Voice), *vizhi* (Eyes), *naadi* (Pulse), *sparisam* (Touch), *malam* (Stools), *moothiram* (Urine) (Selvam et al., 2018). The Siddha system emphasized the individual's diet (*pathyam*) and lifestyles (*Naazhukkam and Kaala -Ozhukkam*) (Durairajan, 1993) since the

effectiveness of the medicines is dependent on the same. All these factors are part of preventive medicine and contribute to strengthening the immune system. Thus, the various stages and symptoms of novel coronavirus infection can be effectively treated with Siddha medicines. According to the Siddha system, Epidemics and Pandemics are stated as "*Uzhi Noi*" or "*Kothari Noi*." At the same time, communicable diseases are mentioned as "*Kollai noigal*" (Durairajan, 1993). These diseases spread widely when the immunity of the individuals is deficient.

In the present situation, preventing the spread of COVID-19 to the third stage (Community spread) warrants equal treatment importance. Though experts advise social distancing, hand washing, and wearing a mask, it is the immunity of an individual that plays a pivotal role in contracting the disease. Some of the Indian herbs, their extracts, and the phytochemicals have been analyzed for antiviral properties. Due to their synergistic action, Siddha medicine formulations act as immune boosters, thus helping the body combatting against invading viruses. Antiviral Siddha drugs, immune-modulatory drugs which are readily employable and which do not require arduous pharmaceutical production, are the need of the hour in the present biosphere of mounting resistance towards antiviral therapy. Many herbal antivirals are reported for various types of virus, and various review articles are published. The mechanism of action and the effectiveness against the novel coronavirus are yet to be explored.

2.4. Classical Siddha formulations and medicines in practice for respiratory ailments

There are various preventive measures and lifestyle habits mentioned in the Siddha system of medicine that effectively prevent respiratory infections.

Siddha drugs like *Nellikai lehyam, Amukkara chooranam, Seenthil chooranam, Triphala chooranam, Vallarai tablets, Nilavembu decoction, Kapha sura decoction, Aya chenduram, Urai maathirai, Bhaavana kadukai,* act as immunostimulants and are in clinical practice. These drugs can be recommended for prevention and during the post-viral convalescence period (Mudhaliyar, 1998). A reasonable number of Siddha formulations effectively treat respiratory ailments like cough, sneezing, bronchial asthma, COPD, sore throat, pulmonary tuberculosis, bronchitis, flu-like illness, and so on. All these are categorized under *Iya noigal* in the Siddha system of medicine. In uncontrollable fever and Pneumonia, the disease *Iya suram* progress to a state called *sanni* (Mudhaliya, 2004). Siddha medicines are classified under internal drugs and external medicines, each consisting of 32 types. *Chooranam* (powder), *kudineer* (decoction), *charu* (leaf juices), *manapagu* (herbal jelly), *rasayanam* (deinties), *lehyam* (electuary), *parpam* (calcinated oxides), *chenduram* (calcinated red oxide) are few forms of internal medicines (Thiyagarajan and Gunapadam, 1981). The drug *adathodai chooranam, adathodai manapagu, thoothulai nei, thoothulai lehyam, thalisathi chooranm, thalisathi vadagam, irumal mathirai, impooral vadagam, velli parpam,* are few medicines that can be co-prescribed with allopathy medicines for cough with phlegm. In dry cough, *athimadhura chooranam, trikadugu chooranam* with ghee works well. To bring down the temperature, *Nilavembu decoction, sarvasura kuligai, linga kattu, thaalaga parpam, velvanga parpam, gowri chindhamani chendurm, pachai karpoora chooranam,* can be recommended for administration (Mudhaliyar, 1998). The safety of the few formulations was already tested by reverse pharmacology in experimental animal models. Furthermore, these formulations are from the books listed in the Drugs and Cosmetics Act. A group of tablets named *Bairava maathirai* is indicated for *Sanni* a complication of extreme toxicity. *Balasanjeevi mathirai* is a formulation that can be safely administered to children. It is also a potent immune modulator (Dayanand Reddy et al., 2019). For headache in viral fever, steam with notchi, manjal, brick can be employed. In Siddhar's masterpiece works, notchi is indicated for cough, bronchial asthma, respiratory diseases caused by an increase in *Iya humor* (phlegm). Consuming *Vitex negundo* leaves grounded and mixed with *Piper nigrum* three times a day will bring down the phlegmatic fever (Pillai, 2006). Turmeric water, Alum water serve as traditional hand sanitizers. Turmeric water is an effective antiviral. The practice of spraying turmeric water is in practice in many Indian villages as a tradition. *Curcuma longa* is one of the ingredients in many Siddha formulations administered for cough and cold. Turmeric powder, when taken with hot milk, brings out the phlegm in the throat. Also, inhaling the smoke from burning turmeric relieves nasal congestion, reduces headache and cold (Pillai, 1948). Neem leaf fumigation will act as an environmental sanitizer.

The strategy of administering immunomodulators for prevention in a risk group, decoctions and herbal preparations in asymptomatic and mild cases, and higher-order medicines in severely infected cases, if followed, will give a promising cure. The taste, potency, and actions of the herbs used in respiratory illness are described in Table 1.

In policy released by Forum of Indian Traditional Medicine (FTIM) on April 5th 2020, AYUSH interventions' scope is dealt briefly, suggesting for change in policies (James, 2020).

Most of the herbs used in Siddha preparations for *Kapha* diseases are of bitter and acrid/pungent taste. In bitter substances, space and air elements are prominent, and astringent is constituted of earth and air elements. *Kapha* humor is a combination of two elements water and earth. The few bitter taste properties with its relevance to *kapha* diseases are a.) bitter reduces all glandular secretions, salivation, and excess body heat. b.) It will improve renal and bowel functions. c.) It will remove toxins from our body. The pungent taste will remove phlegm from the lungs. When taken in the correct quantity, it reduces the inflammatory diseases of the throat (Bhavishya and Haniya, 2016). The properties of these tastes discussed in classical literature correlate with the modern scientific records about the plants mentioned in Table 1.

2.5. Evidences to authenticate the role of alternative therapy in the COVID-19 pandemic

The herbs mentioned and the formulations mentioned are not proved as a treatment for COVID-19 disease. List of Siddha medications towards COVID-19 are discussed in Table 2.

2.5.1. Siddhar Yogam and Varmam

Siddhar *Yogam*, pranayamam contribute evidence as stress reliever and are effective in the management of depression. While teaching to the patients in an isolation ward and home quarantine, the techniques might help them overcome the fear of corona (Kozasa et al., 2008). The common yoga protocol released by the Ministry of AYUSH can be adopted for daily wellbeing (Booklet on Common Yoga Protocol. Ministry of AYUSH, Government of India, 2019). According to sources from the guidelines for Siddha practitioners for COVID-19 released by the Ministry of AYUSH, Government of India, specific *Varmam* points like *Vilangu Varmam*, *Ullangaal Vellai Varmam, Naadi soothira Varmam,* and *Savvu Varmam* boosts the immunity.

2.5.2. Siddha herbo-mineral formulations

A research study has been attempted with the Siddha compound formulations *Gowri chinthamani, Sivanar amirtham, Poorana chandrodayam, Thalaga parpam, Pavala parpam,* and *Vasantha kusumasura mathirai* for screening their antimicrobial activity against *Neisseria mucosa, Klebsiella pneumonia, Streptococcus pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Aspergillus niger* and the use of these formulations in respiratory illness were justified. The drugs *Sivanar amirtham* and *Pavala parpam* have shown microbial sensitivity against all the above tested respiratory pathogens (Rajalakshmi, 2016). Though the antiviral activity against coronavirus has not yet been reported for all herbs, there is evidence for antiviral activities for herbs used in the Siddha formulations, giving hope for herbal practitioners in bringing out the effective drug for COVID-19 disease. Various metabolites like flavonoids, triterpenoids, monoterpenoids, sesquiterpenes, and phenolic and benzoic iridoid glycosides derived from the herbs were responsible

Table 1
Botanical name and properties of medicinal herbs (Mudhaliyar, 2003).

Botanical name	Taste	Potency	Division	Action as per Siddha literature
Vitex negundo	Bitter, Astringent and Acrid	Hot	Acrid	Alterative, Vermifuge, Febrifuge, Expectorant, Diuretic, Astringent, Refrigerant
Curcuma longa	Acrid, Bitter	Hot	Acrid	Carminative, Stimulant, Hepatic tonic
Acalypha indica	Bitter, Acrid	Hot	Acrid	Anodyne, Anthelmintic, Cathartic, Diuretic, Emetic, Expectorant, Emmenagogue.
Piper nigrum	Bitter, Acrid	Hot	Acrid	Acrid, Carminative, Antiperiodic, Rubefacient, Stimulant, Anti-inflammatory, Antidote
Piper longum	Acrid	Hot	Acrid	Stimulant, Carminative, Expectorant
Zingiber officinale	Acrid	Hot	Acrid	Stimulant, Stomachic, Carminative, Sialagogue, Digestive, Rubefacient, Expectorant, Febrifuge.
Solanum trilobatum	Mild Bitter, Acrid	Hot	Acrid	Stimulant, Expectorant, Tonic
Tinospora cordifolia	Bitter	Hot	Acrid	Alterative, Antiperiodic, Aphrodisiac, Demulcent, Stimulant, Stomachic, Tonic, Febrifuge
Phyllanthus emblica	Sour, Acrid, Sweet	Cold	Sweet	Astringent, Refrigerant, Laxative, Diuretic.
Withania somnifera	Bitter	Hot	Acrid	Febrifuge, Diuretic, Alterative, Aphrodisiac, De obstruent, Tonic, Soporific, Sedative.
Anacyclus pyrethrum	Acrid	Hot	Acrid	Stimulant, Sialagogue, Rubifaciant
Adathoda vasica	Bitter	Hot	Acrid	Antispasmodic, Expectorant, Germicide, Diuretic, Febrifuge.
Glyzirihza glabra	Sweet	Cold	Sweet	Emollient, Demulcent, Mild expectorant, Laxative, Tonic
Terminalia chebulata	Astringent, Mild sweet, Sour, Acrid, Bitter	Hot	Sweet	Digestive, Tonic, Expectorant, Febrifuge.
Dryobalanops aromatica	Acrid, Bitter, Salt	Cold	Briskness	Febrifuge, Laxative, Tonic, Coolant, Expectorant.

for the antiviral activity.

An earlier published review article on the pharmacological activities of the ingredients of *Kabasura kudineer* substantiates its use in swine flu (Thillaivanan et al., 2015). Based on the review, *insilco* docking studies on *Kabasura kudineer* for COVID-19 were carried out. An attempt was made to conduct molecular docking research studies of 32 phytochemical constituents from *Kabasura kudineer* and the results showed that there were effective binding interactions with spike protein of SAR-COV-2 for all analogs. It is also reported that Lupeol and Betulin ingredients of the formulation have a hundred percent bioavailability while the other ingredients showed oral bioavailability of less than eighty percentage (Kiran et al., 2020).

A recent finding has stated that the drug *Kabasura Kudineer* enhances immunity and might act as an immunomodulator. The aqueous extract of *Kabasura kudineer chooranam* presented antioxidant activity, anti-inflammatory, antipyretic and antibacterial activity (Saravanan et al., 2017).

An *in-silico* study confirmed that the active molecules from the medicinal plants *Trichosanthes cucumerina*, *Tinospora cordifolia*, *Hygrophilla auriculata*, *Anacyclus pyrethrum, Andrographis paniculata, Adathoda vasica, Saussurea lappa, Clerodendrum serratum, Syzygium aromaticum Zingiber officinale*, which are ingredients of *Kapha sura kudineer* and *thontha sura kudineer* might be responsible for inhibiting the viral pathogenesis at various levels from prevention to cure. *Kapha sura kudineer* showed more inhibitory effect than *Thondha sura kudineer* for coronavirus (Jain et al., 2017). The antiviral activity of *Nilavembu* against the Chikungunya virus was previously established (Kumar et al., 2019). Antipyretic, anti-inflammatory, and analgesic properties of *Andrographis paniculata* were reported, and the compound formulation is currently used as prophylaxis in viral infections (Anbarasu et al., 2011; Rajasekaran et al., 2016). A Prospective case-control with Retrospective data collection on *Nilavembu* consumption was carried out at the National Institute of Siddha. The results have stated that drinking of *Nilavembu Kudineer* as a prophylactic measure markedly prevents fever due to viral infections in all age groups invariably (Christian et al., 2015).

2.5.3. Pharmacovigilance perspectives of Siddha formulations

Any drug with its therapeutic effect has its own side effects when the preparation and prescription are misappropriated. Though there prevails a common thought that AYUSH treatment is safe, it is not so always. The safety of a drug relies on the purification of raw drugs, preparation of the drug as per the prescribed protocol, dose, duration and period of administration, adjuvant used, etc. Toxicity studies have been conducted for numerous Siddha formulations to establish the safety concern. Velmurugan et al. (2017) have reported that the drug *Aya chenduram* is safe up to the dose of 180 mg/kg body weight in animals. The metallic preparation *Gowri chindhamani* is well tolerated in animals up to the dose of 640mg/100 gm b. wt. Acute and subacute toxicity studies on the Siddha drug *Linga kattu* have established its non-toxic nature at the maximum dose of 2000 mg/kg (Shanmugapriya et al., 2014; Ravichandran, 2017). Chitra et al. (2015) have carried out research studies on *Poorna chandhrodhaya chenduram*. The safety of the drug is reported through acute and subacute toxicity studies. Similarly, the compound formulations *Sivanar amirtham, pavala parpam,* and *pachai karpoora maathirai* have been subjected to toxicity studies in animals and were found to be safe (Shunmugaram, 2019; Anbu and Murali, 2018). The earlier published research studies have confirmed the safety of plant-based preparations like *Kabasura kudineer, Nilavembu kudineer, Urai maathirai, Thoothulaathy chooranam, Seenthil chooranam, Triphala chooranam,* etc (Saravanan et al., 2018; Ezhilarasan et al., 2019; Dayanand Reddy et al., 2019; Sofia et al., 2014; Biradar et al., 2007).

2.5.4. Relevant research on Indian medicinal herbs used in Siddha formulations

Vitex negundo is used in decoction preparation and steam inhalation indicated for respiratory illness. Previously in a study conducted by Sangeetha and Rajarajan (2014) the antiviral property of ethanolic extract of the chaste tree leaves was documented. The ethanol extract of the *Vitex negundo* leaves at 31.25 μg/mL concentration inhibited the Asian CHIKV strain. In this study of screening of ethnic medicinal plants for respiratory viruses, *Vitex altissima* (42 μg/mL) showed cytotoxicity against MDCK cells. The study has explored the antiviral potency of *Wrightia tinctoria* particularly against H1NI virus (Maria John, 2014).

Niamsaand and Sittiwet (2009) reported that the aqueous extract of rhizome of *Curcuma longa* at a concentration of 4 to 16 g/L established the Minimum Inhibitory Concentration value and at a concentration of

Table 2
Siddha compounds to treat COVID-19.

Compound	Source	Target/mode of action	Reference
Artemisinin and its derivatives (ARTs)	Artemisia	Blocks tissue fibrosis. Antioxidant and Anti-inflammatory.	Kshirsagar and Rao (2021)
Higher order medicines (a) Iron Bhaspam (b) Silver Bhaspam (c) Gold Bhaspam (d) Copper Bhaspam (e) Zinc Bhaspam	- Incinerated iron -Incinerated silver - Incinerated gold -Incinerated Copper - Incinerated Zinc	• S-protein receptor-binding domain. • Viral genome, Anti- inflammatory • Envelop glycoprotein and S protein, Immunostimulant, Anti- inflammatory • Main protease site of coronavirus at CYS-145 thiolate. Anti- inflammatory • RNA- dependent RNA polymerase. Modulates T-cell mediated immune response.	Sarkar and Mukhopadhyay (2021). Kar et al. (2020) Bafna and Patil (2018) Lv et al. (2014) Niikura et al. (2013)
Herbs	*Glycyrrhiza glabra; Zingiber officinale; Piper nigrum*	- Inhibiting the viral main protease - inhibit binding of S protein and ACE-2 receptor - inhibit viral proliferation	Kumar et al. (2020)
Linga chenduram	Red sulphide of mercury	Strong inhibitory effect on HCV replication	Mysoon et al. (2021)
Oil	*Ficus religiosa,* Sesame Oil	Reduce transmission of virus	Kumar et al. (2020)
Andrographolide	*Andrographis paniculata*	Anti-SARS-CoV-2 Activity	Sa-Ngiamsuntorn (2021)
Chrysoeriol and Luteolin	Phytoconstituents of *Kaba Sura Kudineer*	Spike protein	Kiran et al. (2020)
Ninandrographolide	*Andrographis paniculata*	Immunostimulant	Puri et al. (1993)
SNACK -V	Extracts of 6 plants with 9 phytoconstituents: *Sida acuta, Adhatoda vasica, Andrographis paniculata, Tinospora Cordifolia, Costus speciosus, Plectranthus ambonicus*	Direct inhibition of 2019-nCoV	Kiran et al. (2020)
Kabasura kudineer	Siddha poly herbal formulation	Spike protein	Vincent et al. (2020)
Vasantha kusumakaram mathirai	Herbo metallic formulation	Clinical trial on COVID patients with respiratory symptoms	Chitra et al. (2021)
Thippili rasayanam	Herbal formulation with *Piper longum* as major ingredient	Clinical trial on COVID patients with respiratory symptoms	Chitra et al. (2021)
Adathodai manapagu	*Adadhoda vasica*	Clinical trial on COVID patients with respiratory symptoms Symptomatic Management- Fever and cold	Chitra et al. (2021)

16 to 32 g/L demonstrated Minimum Bactericidal Concentration against the microbes *E. coli*, *Staphylococcus epidermis*, *Staphylococcus aureus,* and *Klebsiella pneumoniae*. Curcumin, the active compound isolated from *C. longa* evinced to be an active compound in inhibiting the HIV-1LTR-directed gene sequencing by not affecting the cell viability (Li et al., 1993). Earlier research reports of Zandi et al. show that curcumin alkaloid and the two derivatives of curcumin, namely gallium-curcumin and Cu-curcumin, revealed notable antiviral activity against Herpes Simplex Virus Type 1 in an *in-vitro* study (Zandi et al., 2010). Curcumin, isolated from the turmeric, was reported to inhibit viral gene expression.

Acalypha indica leaf extracts showed activity against respiratory pathogens *Escherchia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pyogens. Klebsiella pneumoniae* (Thenmozhi and Rajan, 2012).

The extracts of *Piper nigrum* have indicated inhibition on the growth of *Staphylococcus aureus*, followed by *Bacillus cereus* and *Strep. faecalis, Pseudomonas aeruginosa, S. typhi* and *E. coli* Karsha and Lakashmi, 2010). Kim et al. (2012) stated that Piperine derived from *Piper nigrum* and *Piper longum* shows antipyretic, antioxidant, and anti-tumor properties. *Piper longum* fruit oil has demonstrated significant anti-inflammatory activity in rats (Kumar et al., 2009). Piperine alkaloid of pepper and long pepper has been reported for antioxidant activity through its free radical scavenging effect through *in-vitro* and *in-vivo* studies (Mittal and Gupta, 2000). Ali et al. (2008) in their review, documented the pharmacological, phytochemical, and toxicological properties of *Zingiber officinale*. *Chang J S* et al., have concluded that fresh ginger is effective against the Human Respiratory Syncytial Virus and not the dried ones. The fresh rhizome of ginger inhibits HRSV-induced plaque formation in the cell lines HEp-2 and A549 dose dependably. The study also revealed that a high concentration of fresh rhizome of ginger could stimulate mucosal linings to secrete the interferon, IFN-β, which is probably responsible for thwarting viral infection (Chang et al., 2013). *Jung Sang Chang* has again confirmed that dried ginger showed modest antiviral activity, and fresh ginger was effective in the concentration of 10 μg/mL against A549 cells. In a research study, an attempt was made to isolate p-sesquiphellandrene (2) from Ginger, and its *in-vitro* Inhibitory Concentration value (IC) against rhinovirus was reported as 0.44 pM (Clive et al., 1994). Studies on *Zingiber officinale* attribute the antiviral activity to the flavonoid compounds isolated from the rhizome (Denyer, 1994; Bauer, 1976). Krishnan et al. (2009) have reported the antibacterial activity of *S. trilobatum* against various pathogens like *K. pneumonia, S. aureus, E. coli, and P. aeruginosa. Solanum trilobatum* is clinically found to be effective in Bronchial asthma. In continuation of the present study *Govindan* et al., have confirmed that the plant showed improvement in PEFR clinically and signposted an effect on bronchodilation; the oedematous changes in the airway lumen have also reduced. The therapeutic response to *S. trilobatum* corresponds to that of deriphyllin (Govindan et al., 2004). While studying the herb for anti-asthmatic property, aqueous extract and alcoholic extract of the plant *S. trilobatum* at the concentration of 10 and 15 μg/mL reduced the release of Interleukin 1 alpha and further improved the release of Interleukin 8 from the cultured keratinocytes, respectively. Also, the aqueous and alcoholic extracts of the herb *S. trilobatum* when administered for 10 days in animals showed mast cell stabilization at the dose of 10 mg/kg b. w (Ranjith et al., 2010).

A recent study has concluded that *Tinospora cordifolia* could be used as a support medicine to manage HIV/AIDS. It is a potent immune stimulant (Kalikar et al., 2008). The immune-modulatory effects of *Tinospora codifolia* are very well registered through various research studies (Tripathi et al., 1997; Bishayi et al., 2002; Subramanian et al., 2002). Extracts of *Tinospora cordifolia* possess antimicrobial activity against both gram-positive and gram-negative organisms, namely *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris, Enterobacter aerogen, Serratia marcesenses, S. typhi, Shigella flexneri, S. paratyphi, S. typhimurium* (Narayanan et al., 2011; Jeyachandran et al., 2003; Tambekar et al., 2009). Jun--Jiang et al. (2015) have stated that glochicoccinoside D obtained from *Phyllanthus embilica* exhibited strong activity against the H3N2 influenza strain. *Phyllanthus embilica* shows immunomodulatory activity, which is due to its antioxidant property (Liu et al., 2012). Previous research on

Amla has documented its activity against bacteria of the gram-positive and negative strains (Javale et al., 2010; Aneja et al., 2010; Saradha Jyothi and Subba Rao, 2011). *Phyllanthus embilica* is one of the constituents of a Siddha formulation *Triphala chooranam*, an immune modulator (Pranoti Belapurkar et al., 2014). A docking study has shown that *Withania somnifera* can weaken the neuraminidase of the H1NI virus (Cai et al., 2015). Kumar et al. (2018) has reported the effectiveness of using *Withania somnifera* as an adjuvant to enhance the immune system of patients with pulmonary tuberculosis in combination with the DOTS therapy.

Sharma et al. (2010) have reported the immune stimulant activity of *Anacyclus pyrethrum*. *Adathoda* possesses potent anti-inflammatory and antitussive activity (Chakraborty and Brantner, 2015; Dhuley, 1999). The research results carried out by Chavan et al. (2014) revealed that extracts of *Adathoda vasica* have strong activity against the influenza virus, which is demonstrated by inhibiting attachment of virus and/or viral replication. The report suggests the role of the *Adathoda* in viral prophylaxis. They also concluded that Vasicine alkaloids secluded from the leaves' aqueous and methanol extracts might be responsible for the antiviral activity. Methanolic extract of *Adathoda* leaves is also effective against the Herpes virus (Chavan et al., 2013). Duraipandiyan et al. (2015) has recorded that Vasicine acetate got by acetylation of Vasicine derived from *Adathoda vasica* showed moderate antibacterial activity compared to Vasicine. At a dose of 1000 μg/mL, the free radical scavenging activity was recorded. Cytotoxic studies against the adenocarcinoma cancer cell line A549 of lung showed that Vasicine acetate had the half-maximum inhibitory concentration (IC 50) value of 2000 μg/mL. Vasicine acetate may perhaps be furthermore validated in the drug discovery process.

Glycyrrhizin in *Glyzirihza glabra* extract attributes to its antitussive activity (Hikino et al., 1985). Liquiritin, a biologically active compound in the liquorice's methanol extract, impedes capsaicin-induced cough (Kamei et al., 2003). Glycyrrhizic acid found in the *Glyzirihza glabra* inhibits H1N1 virus growth, facilitates virus inactivation, and acts as an immunomodulator (Arora et al., 2011). *Glycyrrhiza glabra* acts as an immune stimulant by stimulating the macrophages (Wagner and Jurcic, 2002). Liquorice is a potent anti-herpes compound too (Badam, 1994).

Lin et al. (2013) have reported that *Terminalia chebula* exhibits antiviral activity against HSV-1 which is probably intermediated through inhibition of initial entry of HSV-1 virus and free virus particle inactivation. In another study, it was reported that the Chebulagic acid and Punicalagin isolated from the herb chebulic myroblan was liable for the antiviral effect against HSV-1 and the possible mechanism of drug action also was dealt (2011). *Terminalia chebula* has shown antiviral activity against the influenza A virus (Badmaev and Nowakowski, 2000).

Camphecene, isolated from *Dryobalanops aromatica* showed the activity against the viruses, influenza viruses A and B in direct hemagglutinin inhibition tests, and trials carried out with mice infected by the influenza virus (Zarubaev et al., 2015).

Apart from herbs, the Siddha system of medicine uses metals, minerals, animal products in medicinal preparations. The higher-order medicines like *Kattu* (Consolidated vermilion), *Kazhangu* (Compound of metallic bodies prepared with mercury and made into pills), *parpam* (Calcinated oxides), *chenduram* (Calcinated red oxide) are used in conditions like delirium, uncontrollable fever, severe infections, etc. The drug's safety lies in proper purification of the ingredients as per literature and correct prescription of dose depending on the body condition of the individual. The diet regimen advised has to be strictly followed.

The exact mechanism of compound Siddha formulations against SARS-CoV −2 is not established. Kadukkai is one of the major ingredients of the drug Triphala chooranam. Chebulagic acid and punicalagin isolated from Terminalia chebula inactivate the free respiratory viral particles and prevent early entry including attachment and penetration phases (Lin et al., 2013). Triphala chooranam which is used for prophylaxis and treatment of infections significantly thwarts elevation of IL-4 levels. It also modifies the decreased IL-2 and IFN-γ levels. The immunosuppressive activity of Triphala is attributed to its inhibitory action on complement system, humoral immunity, cell mediated immunity and mitogen-induced T-lymphocyte proliferation. Research studies shows that the aqueous and alcoholic extracts of the *Terminalia chebula, Terminaia bellerica, Emblica officinalis* enhances the macrophage activation due to their free radical scavenging activity and the ability to neutralize reactive oxygen species Belapurkar et al. (2014). *Nagam* (Zinc) is one of the constituents of Siddha higher order medicines. Zinc is a potent immunostimulant and anti-inflammatory agent. In *parpam* (ashes), zinc is converted into nano size. The anti-inflammatory mechanisms assumed by zinc oxide nanoparticles are inhibition of the NF-κβ pathway and inhibition of mast cell degranulation, inhibition of inducible nitric oxide synthase (iNOS) enzyme expression, inhibition of pro-inflammatory cytokines release and myeloperoxidase inhibition (Kim et al., 2015; Cortese-krott et al., 2014; Klostedudfen and Hauptmann, 1996; Navaei-nigjeh et al., 2018).

3. Conclusion

The Siddha system of medicine has hoarded many experiences in handling endemic/epidemic diseases. There are copious possibilities in the Siddha system in treating this novel coronavirus infection. Accepting Siddha treatments is currently necessary for COVID-19 disease management. Ample support from the Government is essential to prove the Siddha system of medicine's effectiveness against this deadly contagion. Randomized, double-blind trials and placebo-controlled clinical studies are gold standards to offer trustworthy evidence for a particular treatment. Currently, no controlled trials on Siddha medicines in treating SARS-CoV-2 have been published. Further laboratory studies on Siddha medicines may facilitate identifying innovative drugs for fighting coronavirus in human beings to contain the disease. The toxicity studies of the drugs and drug-drug interactions have to be considered while integrating Siddha medicines with modern medicines. In the present crisis, the use of Siddha drugs for patients in isolation, patients having potential risk, asymptomatic patients can be administered with the preventive Siddha drugs. Immune-boosting drugs can be advocated to healthy individuals without any further research. Already the AYUSH hospitals are prepared to accommodate asymptomatic patients. The research evidence and literature evidence that, when made available to policymakers, will introduce Siddha medicines in routine antiviral therapy materialize. On the whole, these historical and published pieces of evidence add strength to Siddha medicine, projecting it as a valuable weapon to fight against coronavirus.

Author contribution

P.Prakash: Conceived of the presented idea. Took the lead in writing the manuscript and wrote the initial draft with the inputs from other authors. Revised the manuscript critically for intellectual content. R. Meena: presentation of submitted draft, contributed in Traditional medicine, activities of herbs, concluding remarks. Revised the manuscript critically for intellectual content. L.Stanley Abraham: contributed about coronavirus, review of manuscript, and critically commented the manuscript. Revised the manuscript critically for intellectual content. Swetha Sunkar: Contributed to reviewing, editing, and proof-reading. Revised the manuscript critically for intellectual content. K.Govindaraju: Contributed to the Introduction section and reviewed and commented on the manuscript. Revised the manuscript critically for intellectual content. Approved the final version of manuscript to be submitted. Durgasruthi Pully: Contributed to the COVID-19 related sections, reviewing, editing, and proof-reading. Revised the manuscript critically for intellectual content. Antony V Samrot: Contributed to reviewing, editing, and proof-reading. Revised the manuscript critically for intellectual content.

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