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## STRATEGIES OF TRADITIONAL SYSTEMS OF MEDICINE COMBATING WITH THE CURRENT PANDEMIC SITUATION OF COVID-19

Deepti Katiyar<sup>1</sup>, Priya Bansal<sup>2</sup>, Manish<sup>3</sup> and Abhishek Kumar<sup>\*2</sup>

Division of Pharmacognosy<sup>1</sup>, Division of Pharmacology<sup>2</sup>, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad - 201206, Uttar Pradesh, India.

ABES Engineering College<sup>3</sup>, Delhi-NCR, Ghaziabad - 201009, Uttar Pradesh, India.

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### Correspondence to Author:

**Dr. Abhishek Kumar**

Assistant Professor,  
Division of Pharmacology,  
KIET School of Pharmacy,  
KIET Group of Institutions,  
Delhi-NCR, Ghaziabad - 201206,  
Uttar Pradesh, India.

**E-mail:** imabhishek12321@gmail.com

**ABSTRACT:** Coronavirus disease (COVID-19) has become pandemic in no time in the world. Understanding the pathophysiological similarities with previously known viruses of the class gave opportunities to explore various molecular targets against COVID-19. Vaccines unavailability propose different research approaches of treatment, including various previously known and some new synthetic molecules, which are also associated with many unwanted effects. Phytochemical compounds and formulations also gain interest in this era, and all the traditional medicine systems were analyzed for any probable therapeutic possibilities. Hence author summarize the various approaches of herbal-based medicine against COVID-19 infection. Ayurveda, Siddha, Unani, Homeopathy, and Chinese medicine systems constitute major traditional herbal-based systems known worldwide. Previous literature were studied to recapitulated findings with modern multi-mechanistic approaches and propose the use of herbals against COVID-19. Scientists are identifying all the possible interventions associated with herbal-based systems to have efficacy against various mechanisms against viral infection. Various herbal extracts and formulations are utilized to increase the human body's immune system to counter the pathophysiological changes due to COVID-19 infections. Promotion of these herbal-based medicines having a positive impact on the immune system is essential now. The review discussed the old and novel approaches revealing the efficacy of different phytoconstituents and herbal-based medicines against COVID-19. This review briefly highlighted the use of traditional herbal-based medicine systems against the novel coronavirus utilizing the modern approaches of multi-mechanistic targeting. A thorough investigation of different formulations from these systems is warranted through clinical studies for their global acceptance.

**INTRODUCTION:** Increased understanding of genetics and virology revealed that similar pathogenicity shared by the three most severe coronavirus species SARS-CoV-2 (COVID-19), SARS (Severe Acute Respiratory Syndrome), and MERS (Middle East Respiratory Syndrome)

resulting in similar symptoms profile of fever, cough, headache, fatigue, and shortness of breath that may progress to pneumonia, pulmonary embolism, organ failure, and even death<sup>1,2</sup>.

In addition, novel drug discovery approaches including, homology modeling and virtual screening, applying protein crystallography data to determine molecules of interest against SARS-CoV-23. The available drugs can be screened targeting different proteins involved in coronavirus adherence to human cells, viral replication, and various molecular functions. Viral spike (S) glycoprotein interaction with angiotensin-

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converting enzyme 2 (ACE-2) in the lung tissue that is resulting in severe inflammation and vascular permeability are well-reported targets for researchers<sup>4</sup>. Viral capsid associated proteins like Spike, nucleocapsid (N), envelop (E), and membrane (M) glycoproteins with many accessory proteins comprise the attachment, viral replication, virions maturation, and further infection severity of SARS-CoV-2<sup>5</sup>. Researchers have evaluated various flavonoid and non-flavonoid based natural products against viral fusion and interaction with human ACE-2 receptor<sup>6</sup>. Previously available antiviral and antimalarial drugs are extensively studied against different viral targets to interfere with viral fusion and replication with promising results. Still, in many cases, the pharmacological limitation of using broad-spectrum antiviral and antimalarial has proven to be ineffective<sup>7, 8</sup>. Currently, many targets are under extensive studies resulting in the repurposing of available molecules from natural products. Utilizing virtual screening methods, Vardan and Sahoo have investigated 18 naturally occurring potential ligands and found limonene and other compounds with interactive capacity (docking score-based) against S-protein, ACE-2, and RNA-dependent RNA polymerase<sup>9</sup>.

Being a  $\beta$ -coronavirus SARS-CoV-2 on transcription produces large polypeptides which are cleaved by different proteases to produce desired proteins<sup>10</sup>. SARS-CoV-2 possesses Papain-like protease (PLpro) and Main protease (Mpro), also known as 3-chymotrypsin-like protease (3CLpro), facilitating the cleavage of polypeptide<sup>11</sup>. Small proteins produced by Mpro and PLpro mainly contribute to the generation of RNA polymerase, endoribonuclease, exoribonuclease, and other functional proteins contributing to complicated viral RNA replication and maturation of virus<sup>11-13</sup>. Many researchers have screened different herbal extracts and phytochemicals against Mpro and PLpro. Previously, the presence of an apigenin moiety at position C-3' of flavones, as biflavone in the leaf extract of *Torreya nucifera* had a Mpro inhibitory efficacy<sup>13</sup>. Further, constituents obtained from fruit extract of *Paulownia tomentosa* tree are capable of targeting PLpro<sup>11</sup>. Chandel and coworkers screened 19 phytoconstituents against Mpro and revealed an inhibitory potential and best ADME properties in Rhein, Withanolide D, Withaferin A, Enoxacin, and Aloe-emodin<sup>14</sup>.

Coronaviruses are large enveloped viruses with RNA as genetic material. In addition to all probable targets discussed above, drug targeting to the RNA replication is a potential drug development approach. RNA-dependent RNA polymerase (RNAP) is an essential enzyme for viral replication<sup>15</sup>. Targeting RNAP can bring vital changes that hinder the replication of RNA from RNA template (transcription) in CoV-2 virulence<sup>16</sup>. Earlier, various RNAP inhibitors are developed as successful antiviral candidates against RNA viruses<sup>17, 18</sup>.

Researchers utilized virtual screening tools to investigate various phytochemicals from traditional Chinese medicines and reported potency of theaflavin, quercetin and kaempferol against RNAP and proposed for further antiviral evaluation of these compounds counter to CoV-216,<sup>19-21</sup>. Targeting RNA replication may interfere with virion assembly formation and further viral release. Like RNAP, viral helicase (a non-structural protein) is also an important component of RNA replication<sup>22</sup>. Sensing the need of this era, the curiosity of researchers, new drug approaches are implemented utilizing available knowledge to explore drugs that can control the SARS-CoV-2 infection to control pandemic conditions until a vaccine can be made available.

Further, studies have suggested herbal medicines as sources of a suitable new drug or feasible alternatives to resistant-viable drugs against viral disease<sup>23</sup>. Emphasizing the prevention of previous viral infections of SARS, other viral diseases, Chinese herbal medicines were suggested as an auxiliary approach against SARS-CoV-2<sup>24</sup>. Ang and coworkers evaluated 28 traditional herbal formulations to be used against CoV-19 on the basis of available guidelines. They revealed that *Glycyrrhizae Radix et Rhizoma*, *Armeniacae Semen Amarum*, *ephedrae Herba*, and *Gypsum Fibrosum* are mostly used in these guidelines. Various studies suggested the lacking of clinical evidence to warrant the efficacy of traditional medicine. The Indian traditional system of medicine (Ayurveda and Siddha), the Unani medicine, and the Chinese herbal medicine system provide herbal preparations effective against various ailments, including viral infections<sup>25, 26</sup>. Phytoconstituents specified in the literature are

identified and evaluated for efficacy against various infectious diseases<sup>27</sup>. Further, many treatment formulas and protocols based on Chinese herbal medicines are also investigated for preventive and curative measures against CoV-2 infection<sup>27, 28</sup>. More trial-based evidence is required for these herbal-based preparations and specific phytoconstituents to make them globally accepted. In this review, we summarized the molecular aspects of phytoconstituents and traditional medicinal systems to evident their efficacy against molecular targets of CoV-2. The phytoconstituents are proposed with promising antiviral activity through variable mechanisms and are recommended further for preclinical and clinical studies for their safe and effective use in clinical practices.

**2. Methodology:** The literature of traditional medicine is as old as human civilization. But pharmaceutical advances and scientific evidence are available since about two centuries. Authentic and reputed scientific search engines including Web of Science (<https://webofknowledge.com>), Google Scholar (<https://scholar.google.com/>), Pubmed Central (<https://www.ncbi.nlm.nih.gov/pmc/>), Medline (<https://www.nlm.nih.gov/>), Scopus (<https://www.scopus.com>), and Science Direct (<https://www.sciencedirect.com>), were utilized for detailed literature survey.

A detailed bibliographic search was performed using these databases on different traditional medicine systems and all the approaches against viral infections. The literature survey includes published books, reports, conference proceedings, and articles in peer-reviewed journals from 1991 till 2020 that include reports of texts available on traditional medicines from many decades. After assessment of more than 200 literatures a total of 91 full-text references were included in this manuscript to summarize the correlation of phytoconstituents and herbal-based medicine systems with severe viral infections, including COVID-19.

Various interventions of traditional medicine systems and newer approaches of modern pharmacology are reviewed to explore the multi-mechanistic approaches of phytoconstituents against COVID-19 infection. Although the literature on herbal-based medicines and their antiviral efficacy is wide evidence but we tried to

conclude the important implications related to combating COVID-19 conditions.

### 3. Strategies Adopted by Traditional Systems of Medicines against Covid-19:

**3.1 Ayurvedic System of Medicine:** Ayurveda mentions the concept of epidemics under the term of Janapadodhwamsa<sup>30</sup>, explaining that some disruption in the balance between Vayu (Air), Jala (water), Desha (habitat), and Kala (seasons) results in such diseases which kill mass of people. Thus, the Ayurvedic interventions have been explored for the prophylaxis, treatment, and management of COVID-19<sup>31, 32</sup>.

The Ministry of AYUSH, Government of India, has issued the guidelines for enhancing the immune system to combat the pandemic viral disease, which includes preventive health manoeuvre like general measures (drinking warm water; practicing yogasanas; adding spices like turmeric, coriander, cumin, and garlic while cooking food); ayurvedic immunity promoting measures (taking Itsf of Chyavanprash in the morning; drinking herbal tea made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a daily and golden milk); Simple Ayurvedic procedures (Nasal application and oil pulling therapy) and steps to be taken during dry cough/sore throat (Steam inhalation with Pudina (Mint) leaves or Ajwain (Caraway seeds) and Lavang (Clove) powder with honey)<sup>33</sup>. In addition to these guidelines, an expedient and tenable action plan for Ayurvedic involution has been presented for people under the following four categories<sup>32</sup>:

**(1) Unexposed Asymptomatic Group:** This group includes basically the healthy people who neither exhibit any type of symptoms nor have any associated risk factor, and they are most appropriate for strengthening the immune system.

Here the pharmacological and non-pharmacological approaches are included as precautionary measures. A healthy lifestyle, adequate sleep, ample of physical activity, care of suppressible and insuppressible impulses, sadvritta (equilibrium between body, mind, social and spiritual well-being) and social distancing from the infected persons is important<sup>34</sup>.

**(2) Exposed asymptomatic (Quarantined):** The Quarantined group consists of such people which do not manifest any symptoms but have a contact history. These can be prevented from the infection by giving Sanjeevani vati (consisting of 10% each of *Embelia ribes*, *Acorus calamus*, *Tinospora cordifolia*, *Semecarpus anacardium* and *Aconitum ferox* widely used in fever due to infection and also in communicable diseases)<sup>35</sup> and Chitrakadivati (consisting of 6.66% each of *Plumbago zeylanichum*, *Apium graveolens*, *Piper nigrum* and *Piper chaba*) and a blend of Guduchi (*Tinospora cordifolia*), Haridra (*Curcuma longa*) and Shunthi (*Zingiber officinale*). This option targets to conserve the agni and aam pachana so that the progress of pathogenesis can be stopped in its primary sanchayaprakopa-prasara stage<sup>36</sup>. This group may also be administered with decoction containing some antivirals and broad-spectrum protease inhibitors like *Zingiber officinale*, *Curcum longa*, *Tinospora cordifolia*, *Ocimum sanctum*, *Adhatoda vasica*, *Glycyrrhiza glabra*, *Swertia chirata*, *Andrographis paniculata*, *Moringa oleifera*, Trikatu (composed of dried *Zingiber officinale*, *Piper nigrum* and *Piper longum*) and Triphala (composed of *Emblia officinalis*, *Terminalia bellerica*, *Terminalia chebula*)<sup>37-39</sup>.

**(3) With Mild COVID-19 symptoms:** This group includes SARS-CoV-2 positive people exhibiting mild Upper Respiratory Tract Infection. They should be cautiously isolated and observed for any progress of the disease. An adequate therapy should be given to them in order to stop the symptoms and balance the disturbed doshas. Ayurvedic formulations such as *Lakshmi Vilas Rasa*<sup>40</sup>, *Sanjeevani vati*<sup>35</sup>, *Pippali rasayana*<sup>41</sup>, *Chitrakadivati*, *Vyaghri haritaki*, *Gojihvaadi kashaya*, *Kantakaari avaleha*, Talishadi, Dashamulkwath, Sitopaladi<sup>42</sup> and Yashtimadhu may be administered to patients in this stage. Those patients exhibiting the progression of infection may be quickly shifted to ICU<sup>25</sup>.

**(4) With Moderate to Severe COVID-19 Symptoms:** This group consists of patients with high risk. Along with tertiary care, the victims can be given Ayurvedic medicines to decrease the impact of pathology and secure more time for intensive control<sup>43</sup>, *Pippali rasayana*<sup>41</sup>, *Sanjeevanivati*, *Laghu Vasant Malati*, *Tribhuvan*

*keerti rasa*<sup>44</sup>, *Mrityunjaya rasa*, *Brihata Vata Chintamni rasa*, and *Siddha Makardhvarajasa* are few of the Ayurvedic formulation which can be given during this stage. The *Rasaushadi* show enhanced bioavailability due to the nanosize of their particles<sup>45</sup>.

Besides the above plan, the Ayurveda professionals should be properly trained for screening the people for associated risk factors. They should also be provided with modern personal protection equipment and access to diagnostic facilities. Good networking of AYUSH healthcare authorities with local health authorities may help effective utilization of human resources in the AYUSH community during the current crisis<sup>46</sup>.

**3.2 Unani System of Medicine:** The Unani System of Medicine refers to an epidemic as waba, which is thought to occur if such contagion or ajsam-i-khabitha find a place in air or water<sup>47</sup>. It has also been stated that most epidemics develop in autumn season, especially if the preceding summer season was humid and the wind is still<sup>48</sup>. Ibn Sina (980–1035 CE) stated, “epidemics spread from one person to another, and one city to another like a message”<sup>47</sup>. Zakariya Razi (865–925 CE) stressed this fact and stated, “there will always be something common in patients of epidemics, whether a place, food, drink or travel history”<sup>49</sup>. Thus, these Unani practitioners stressed on the fact that the transmission occurs through fomites. Although the microbial studies are not mentioned in this traditional system of medicine yet the Unani scholars could imagine and understand the concept of microorganisms transmitting the infections and transforming into epidemics<sup>50</sup>.

Apart from isolation and quarantine, the epidemic management in Unani medicine includes the following measures:

**(i) Sanitization of Surroundings:** During the epidemic, the sanitization of the surroundings is very important because it is the channel that eases the spread of infection. The Unani texts mention the usage of medicinal herbs as decoction or distillate for spray (e.g., vinegar from sugarcane, *Saccharum officinarum*) or as fumigants (e.g., sandalwood - *Santalum album* and camphor - *Cinnamomum camphora*) to make the air free from

impurities<sup>50</sup>. Zakariya Razi enlists the aromatic drugs used as fumigants during epidemics such as, loban (*Styrax benzoides*, mastagi (*Pistacia lentiscus*), izkhar (*Cymbopogon jwarancusa*, zanjabeel (*Zingiber officinale*), sibr (*Aloe vera*), and za'fran (*Crocus sativus*)<sup>49</sup>. There is not much scientific data revealing the use of volatile oils as fumigants. The theory behind using essential oils for this purpose might be their antimicrobial potential due to their alcoholic content<sup>51</sup>.

**(ii) Dietary Modifications:** During the situation of epidemics, it is advisable not to eat meat, sweets, and fruits with higher water content. Fish should be avoided entirely. The meat of birds found on the mountain may be consumed.

The reason being that the animals staying on land or water are more likely to be infected than those found at higher altitudes. Intake of citrus fruits such as lemon, oranges, and grapes is advisable. Oxymel (a mixture of honey and vinegar) containing Arq-e-gulab (rose water) has been suggested to provide protection during epidemics<sup>48, 52</sup>. Fasting, overeating, and dry throat may cause adverse effects on the bodily constitution<sup>47</sup>.

**(iii) Health Promoting Herbs:** The Unani Practitioners have prescribed single herbs as well as a combination of herbs for the protection of health during an epidemic. The following drugs have been advised:

(a) Antimicrobial drugs like Sirka (Acetic acid-vinegar)<sup>48, 53</sup>, Turanjabeen (*Alhagi pseudalhagi*)<sup>54</sup>, Anar (*Punica granatum*)<sup>52, 55</sup>, Revand Chini (*Rheum austral*)<sup>56</sup>, banafsha (*Viola odorata*)<sup>57</sup>.

(b) Immunomodulatory herbs like Amaltas (*Cassia fistula*)<sup>52, 58</sup>, Za'fran (*Crocus sativus*)<sup>59</sup>.

(c) Anti-inflammatory agents such as Toot (*Morus nigra*)<sup>48, 60</sup>, Revand Chini (*Rheum austral*) (Pandith et al., 2018), Imli (*Tamarindus indica*)<sup>61</sup>.

(d) Antioxidants like Arq-e-Gulab (*Rosa damascene*)<sup>48, 62</sup>, Anar (*Punica granatum*)<sup>52, 55</sup>, Amaltas (*Cassia fistula*)<sup>58</sup>.

(e) Anti-pyretic drug like Turanjabeen (*Alhagi pseudalhagi*)<sup>54</sup>.

(f) For respiratory diseases, a solution of sumaq (*Rhus coriaria* L., decoction), rub-e-toot (*Morus*

*nigra* L.), rub-e-jauz (*Juglans regia* L.), and arq-e-gulab (*Rosa damascene*) before sleep is advised<sup>48</sup>.

Considering the above facts, the Unani System of Medicine has summarized the following measures for symptoms of COVID-19, which resemble those of nazla-e-wabaiya mentioned Unani literature:

**(a) Preventive Measures:** General measures of isolation, quarantine, and social distancing must be followed. Infected persons should take precautions while sneezing or coughing.

Sanitization of environment, dietary modifications and health-promoting herbs should be used as mentioned above<sup>50</sup>.

**(b) Proposed Management:** Al Asbab wa-Alamat prescribes the care of nazla-e-wabaiya through immunomodulatory, anti-inflammatory, and antipyretic drugs like the decoction of Unnab (*Ziziphus jujube* Mill., Rhamnaceae) 5 no., Behidana (*Cydonia oblonga* Mill., Rosaceae) 3g, Sapistan (*Cordia dichotoma* G. Forst., Boraginaceae) 9 no., and Khaksi (*Sisymbrium adenophorum* Tidestr., Brassicaceae) 5g. If the patients suffer from associated diarrhea, habb-ul aas (*Myrtus communis* L., Myrtaceae) and tabasheer (*Bambusa bambos* (L.) Voss, Poaceae) are also given. To allay thirst, Sheera tukhm e kahu (*Lactuca sativa* L., Compositae, seed paste) may be advised.

In case of pneumonia or pleurisy, *Aloe vera* L. sap (1 g), qairooti aarad karsana (10 g), *C. sativus* L. stamen (1g) are compressed, mixed, warmed moderately and applied on the chest and shielded with a cotton bandage<sup>63, 64</sup>. A polyherbal Unani formulation - Qairooti aarad karsana consisting of Aarad e Karsana (*Pisum sativum* L., Leguminosae, flour), Aarad e Hulba (*Trigonella adscendens* (Nevski) Afan. & Gontsch., Leguminosae, flour) - 60g each, Kalonji (*Nigella sativa* L., Ranunculaceae, seeds), Asl-us-Soos (*Glycyrrhiza glabra* L., Leguminosae, root) - 24 g each, Aqarqarha (*Anacyclus pyrethrum* (L.) Lag., Compositae, root) - 18g, Roghan-e-Sosan (*Iris ensata* Tunb., Iridaceae, oil) and Bees Wax- both in equal amount, quantum satis, to make a paste is given for chest diseases<sup>65</sup>.

**3.3 Homeopathy System of Medicine:** Previously, the uses of homeopathic intervention as preventive measure in various viral infections are evident<sup>66</sup>. Understanding the pathophysiology and studies of various clinical cases helps to establish a correlation of symptoms with the extent of infection. The collected information can be utilized to discover specific homeopathic treatment regimen suitable for patient's condition<sup>67, 68</sup>. Based on the evidences of prophylactic and curative homeopathic medicine's efficacy against previous viral epidemics like Spanish influenza, yellow fever, scarlet fever *etc.*, proven<sup>66, 68</sup>. Specific observations and studies on symptoms and particular patient conditions in various cases produce sufficient information on the homeopathic system's efficacy against several epidemic diseases<sup>69, 70</sup>. Clinical trials associated with specific viral infections and the efficacy of homeopathic medicines revealed a successful benefit in the health and recovery process<sup>71, 72</sup>. Considering all previous studies facts and outcomes, homeopathic medicine system is suggested as adjuvant approaches along with critical care of COVID-19. Homeopathic medicine Arsenicum Album-30 is a preventive care drug for flu-like symptoms of COVID-19. Scientific publications from the Ministry of AYUSH and other government issue notes and guidelines on the utility of homeopathic medicine-induced preventive actions against infective disease by boosting immunity and reducing pathophysiological interventions<sup>73-76</sup>.

**3.4 Traditional Chinese Medicine:** The involvement of traditional Chinese Medicine can help to decrease the severe symptoms of patients suffering from infectious diseases. The strategy for the management of viral infection involves the following:

**(1) Prevention:** According to TCM, Qi is the fundamental substance constituting the human body responsible for maintaining the primary functions. Thus, there are two types of Qi. Healthy Qi mentions the substances which maintain the normal functions of the body. Pathogenic Qi includes unhealthy matter.

As the lungs are very delicate, firstly, their function gets affected. The clinical evidence of COVID-19 patients classify 'wet', 'heat', and 'congestion' in

their lungs. 'Wet' refers to component with sticky and heavy turbidity resulting into long duration of disease and damaging the lung function. 'Heat' cites the element with hot, dry, and rising turbidity that can produce the disease. 'Congestion' is an actuating component that can obstruct blood circulation and can result into manifestations such as pain.

Thus, the preventive strategy of TCM targets to protect the lungs. Yupingfeng San<sup>77</sup>, is a traditional Chinese herbal formula used to protect lung Qi and avoid pathogenic Qi. This formulation comprises of 20 g Astragalus, 15 g Fanfeng and 15 g Atractylodes. These three herbs are mixed and boiled together in 1000 ml pure water. These are boiled to obtain 600 ml of the tincture. It is then given in the dosage of 200 ml orally once, three times a day. Earlier studies have exhibited that this formulation could manage the immune function of the body. Astragalus can upgrade lung Qi and can decrease phlegm. Fangfeng can alleviate the pathogenic Qi, remove dampness and allay pain. Atractylodes strengthen the spleen Qi, which can influence digestion and absorption<sup>8</sup>.

**(2) Treatment of Mild Infection:** Fever, sweat, headache, cough, sore throat, thirst, red tongue tip, thin white or pale-yellow coating, and floating pulse are symptoms of mild infection. As per TCM theories, the pathogenic Qi, damages the lung Qi. The disruption in lung Qi results in lung heat and dampness, causing the typical symptoms of fever, sore throat, cough, and fatigue. So, such herbal formulations are used in mild infections, which can 'clear the lung heat and dampness' to heal it. Sangju yin and Yinqiao san are prescribed for clearing the lung heat, removing phlegm, soothing cough, regulating the lungs, and restoring normal lung function. Clinically Sangju yin is prescribed for patients with severe cough and Yinqiao san for patients with a high fever.

The formula of Sangjuyin consists of Mulberryleaf 15 g, Mint 6g, Chrysanthemum 10 g, Forsythia 10 g, Chinese bellflower6g, Reed root 15 g, Almond 9 g, and Licorice 3 g. Yinqiao contains san Forsythia 15 g, Burdock 6 g, Bamboo leaves 6 g, Chinese bellflower6g, Mint 6 g, Honeysuckle 15 g, Licorice 3 g, Nepeta 6 g, and Lighttempeh 5 g. The medicinal herbs are mixed and boiled together in

1000 ml pure water. These are boiled to obtain 600 ml of the tincture. They are then given in the dosage of 200 ml orally once, three times a day 8.

Few research investigations have also revealed that Yinqiao san may have antibacterial and antiviral activity. It may also improve the immune function of the upper respiratory tract <sup>78</sup>.

**Treatment of Severe Symptoms:** The National Health Commission and the National Administration of Traditional Chinese Medicine of the People's Republic of China developed clinical guidelines for the management of COVID-19. If the infection could not be managed in mild condition, then the manifestations of infectious patients involve high fever, cough, phlegm, difficult breathing, sweating, chest tightness, fatigue, nausea, bloating, red or dark red tongue, yellow coating, slippery or weak pulse, failure of the respiratory system and other vital organs resulting into death. As stated by TCM, if primary care is ineffective, or the pathogenic Qi is too powerful, the healthy Qi will be impaired seriously, and lungs will stop functioning. The sputum will be produced increasingly, and the patient will be unable to breathe. Maxingshigantang (decoction) and Baihegujin tang can be used to comfort the healthy Qi, remove the pathogenic Qi and assist the lung to get rid of sputum and receive air <sup>8</sup>.

Maxingshigan tang comprises Ephedra 15 g, Almond 10 g, Licorice 9 g, and Plaster 20 g. The formula for Baihegujin tang contains Shudihuang 15 g, Xuanshen 10 g, Dihuang 15 g, Angelica 15 g, White peony 6 g, Chinese bellflower 6g, Beimu 6 g, Licorice 3 g, Ophiopogon 6 g, Lily 6 g. These medicinal herbs are mixed and boiled together in 1000 ml pure water. These are boiled to obtain 600 ml of the tincture. They are then given in the dosage of 200 ml orally once, three times a day. Maxingshigan tang is basically used to clear lung fever and decrease phlegm. Baihegujin tang can revitalize the lung Qi. These two formulations are mixed together in case of severe infection, which results into healthy Qi and removal of the pathogenic Qi <sup>8</sup>.

**4. Recent Evidence of uses of Herbs for Covid-19:** Currently, many research investigations are being carried out for finding the most potent drug candidate for COVID-19.

A review by Boone and Custonic, has stated the utility of herbs to combat COVID-19. Vitamin C (from oranges, kiwi, kale, and broccoli), Magnesium (from black beans, avocado, and whole grains), Moringa, Reishi, and Curcumin can be taken to augment our immune system. The natural drugs which can be beneficial for our respiratory system are licorice, sage, thyme, garlic, ginger, cinnamon, honey, orange, and marshmallow roots. Eucalyptus and sage infusion can be used in the form of inhalation for respiratory troubles. Eucalyptus, mullein, sage, garlic, licorice, and thyme have been reported to alleviate the symptoms of cough, shortness of breath, and pneumonia. Feverfew, yarrow, chamomile, holy basil, turmeric, nettle, and clove given in the form of tea/infusion/capsules exhibit anti-inflammatory properties. The study has also stated that most of the herbal drugs can be taken in the form of an infusion, decoction, extract, tincture, pills, capsules, pastilles, syrup, or honey infusion. Velvet tea (decoction of marshmallow root and licorice) is also highly beneficial <sup>80</sup>.

Patanjali has proposed a treatment regime for the treatment of COVID-19. This includes few herbal medicines in combination with ICMR approved hydroxychloroquine. All these drugs were investigated for their potential against COVID-19. To search for most suitable herbal drug, more than 1000 phytoconstituents were screened *in silico*. They were studied for their binding affinities to COVID-19 essential proteins and host protein interactions. The study revealed that withanone from Ashwagandha, tinocordiside from Giloy, and scutellarein from Tusli docked very well in the bonding interface of ACE2-RBD complex <sup>81</sup>.

FDA-approved antiviral phytochemicals were screened using PyRx virtual screening tool targeting the proteases of SARS-CoV-2. The study revealed that Rhein (-8.1) WithanolideD(-8), WithaferinA (-7.7), Enoxacin (-7.4), and Aloe-emodin (-7.4) exhibited ADME characteristics. Thus, these Phytoconstituents may be utilized as probable inhibitors against SARS-CoV2 Main Protease after their proper validation <sup>14</sup>.

In another *in-silico* study, the potential of few herbal compounds was compared against COVID-19. Molecular docking analysis was done through

AutoDock Vina, and the most suitable ligand was recognized on the basis of their binding energy. The research concluded by stating that ‘Quercetin, Hispidulin, Cirsimaritin, Sulfasalazine, Artemisin, and Curcumin exhibited better potential inhibition than Hydroxy-Chloroquine against COVID-19 main protease active site and ACE<sup>82</sup>.

Research screened the potency of phytochemicals from Curcuma sp., Citrus sp., *Alpinia galanga*, and *Caesalpinia sappan* against SARS-CoV-2 through molecular docking using the MOE 2010 program. The study concluded indicating that flavonoids from Citrus sp. followed by galangin from galangal, brazilin from sappan wood, and curcumin from Curcuma sp exhibited potential as SARS-CoV2 inhibitor. Thus, these drugs can be consumed in daily life for prophylaxis of COVID-19<sup>83</sup>.

Another recent study against the viral receptors using the molecular docking technique identified 6-gingerol as an excellent phytochemical possessing remarkable pharmacokinetic properties with the highest binding affinity ranging from -2.8764 KJ/mol to -15.7591 KJ/mol with various COVID-19 viral protein targets. Thus, 6-gingerol from ginger could be used a potent medicine for COVID-19<sup>84</sup>.

Hesperidin, naringin, and pectin from citrus peels have also proved their potency against COVID-19 through a recent computational and experimental study<sup>85</sup>.

Further, the compounds from *Nigella sativa* underwent docking studies through Molecular Operating Environment Software (MOE). The results were stated as “Nigelledine docked into 6LU7 active site gives energy complex about -6.29734373 Kcal/mol which is close to the energy score given by chloroquine (-6.2930522 Kcal/mol) and better than energy score given by hydroxychloroquine (-5.57386112 Kcal/mol) and favipiravir (-4.23310471 kcal/mol).

Docking into 2GTB active site showed that  $\alpha$ -Hederin gives an energy score of about -6.50204802 kcal/mol, which is a better energy score given by chloroquine (-6.20844936 kcal/mol), hydroxychloroquine (-5.51465893 kcal/mol) and favipiravir (-4.12183571 kcal/mol).” Nigellidine and  $\alpha$ -Hederin from *Nigella sativa* emerged to be

the most suitable drug candidate against COVID-19. A study expressed that the use of drugs such as *Zingiber officinale*, *Scutellaria baicalensis*, *Nigella sativa*, *Hypericum perforatum*, *Glycyrrhiza glabra*, *Echinacea* spp., *Camellia sinensis*, and *Allium sativum*, can help in improving the immune response. The phytoconstituents from these plants have shown inhibitory effects against the various targets of corona virus-like S protein. They can also restrain the replication of many viral enzymes like helicase, Plpro, 3CLpro, etc.<sup>87</sup>

Additionally, the in silico evaluation of the constituents of essential oils of Eucalyptus and Corymbia species such as eucalyptol, 3-carene, alpha-terpineol, citronellol, d-limonene, o-cymene, and alpha-pinene showed that these phyto-molecules can be utilized as a potent inhibitor of coronavirus<sup>88</sup>.

A recent study concluded that glyaspein, isorhamnetin, acetoside, and numerous flavonoids might be beneficial in the management of COVID-19 by a reduction in the cytokine storm of the host, controlling the immune reaction and safeguarding the organs<sup>89</sup>.

One of the strategies for the management of infection due to coronavirus state that the drugs and herbs should be given along with the balanced diet, nutraceuticals, nutritional supplements, vitamins and micronutrients. This would help in decreasing hospitalization and complications of the respiratory system<sup>90</sup>.

Likewise, two different computational studies on phytoconstituents from official Siddha formulations: Nilavembu kudineer (Mentioned in the Siddha text Siddha Vaithiya Thirattu effective against Dengue and Chikunguniya virus)<sup>91</sup> and Kabasura Kudineer (used in treating viral fever and respiratory diseases)<sup>92</sup> have also been carried out. The results revealed that Benzene 123 Triol from Nilavembu Kudineer Chooranam could bind against the ACE2 receptor with a low glide score of -6.185 Kcal/mol. The *in-silico* analysis of Kabasura Kudineer showed that nine compounds possessed high binding affinity<sup>92</sup>.

Ma Xing Shi Gan Decoction (MXSGD) – a combination of modern medicine and TCM was investigated for its mechanism for the treatment of



COVID-19. Around 97 active components were screened, and 169 targets were projected. Some of these included Heat shock protein-90, RAC-alpha serine/threonine-protein kinase, Transcription factor AP1, Mitogen-activated protein kinase1, Cellular tumor antigen p53, Vascular endothelial growth factor A and Tumor necrosis factor. The study concluded by stating, “The therapeutic mechanisms of MXSGD on COVID-19 may primarily involve the following effects: reducing inflammation, suppressing cytokine storm, protecting the pulmonary alveolar-capillary barrier, alleviating pulmonary oedema, regulating the immune response, and decreasing fever”<sup>93</sup>.

Respiratory Detox Shot, a lung toxin dispelling formula based on TCM was investigated in a study for its mechanism of action. TCM databases revealed the presence of 1071 known phytochemicals from the nine ingredients. Of these 157 qualified the drug-likeness screening and exhibited 339 anticipated targets in the constituent network. The molecular docking utilizing computational pattern recognition revealed that 118 phytochemicals showed a high binding affinity with SARS-coronavirus-2, 3-chymotrypsin-like protease (3CL pro). The 3CL inhibition assay was used to validate the in vitro activity of 22 phytoconstituents of RDS. The study concluded that RDS may be used in general treatment for early stages of COVID-19<sup>94</sup>.

An Ayurvedic Text has mentioned the use of herbal preparation containing *Zingiber officinale* and *Citru medica* for nasal rinse to manage the contagious fevers. Keeping this fact in mind, a in silico study was conducted to explore the potential of the components of these herbs in management of COVID-19. The findings revealed that the Phyto molecules in these plants had an attraction for virus spike protein and host's ACE-2 receptor. This would finally lead to the decrement of viral load and detaching of SARS-CoV-2 from the nasal passages<sup>95</sup>.

Balkrishna et al., have reported that a herbal preparation consisting of extracts of *Tinospora cordifolia*, *Withania somnifera*, and *Ocimum sanctum* might be beneficial against SARS-CoV-2. The computational studies have revealed that the phytochemicals of herbs present in coronil could

inhibit the entry of SARS CoV-2 into the host cell and related cytokines' production. It could hamper the interface of ACE-2 with SWT (wild-type S protein) and also with SD614G (more infectious variant). The elevated level of IL-6, IL-1 $\beta$ , and TNF- $\alpha$  in A549 cells also reduced after treatment with Coronil<sup>96</sup>. In another research investigation, Balkrishna et al., performed the analytical evaluation of Divya-Swasari-Vati, which is a herbal medication containing calcium prepared for providing relief from the respiratory symptoms due to corona infection. The study identified and quantified eleven active marker phytochemicals gallic acid, methyl gallate, coumarin, protocatechuic acid, ellagic acid, cinnamic acid, protocatechuic acid, glycyrrhizin, glabridin, eugenol, piperine and 6-gingerol<sup>97</sup>. Additionally, Balkrishna et al., conducted a survey to study the satisfaction of patients for Divya-Swasari-Coronil-Kit Against COVID-19. The study concluded that this kit possesses a positive and valuable inference on psychosomatic wellbeing and Quality of life<sup>98</sup>.

Although, an array of herbal drugs has been suggested to be safe and efficacious for the management of COVID-19, but a research investigation targeted to unveil the associated toxic effects of some of these herbs such as Oleandrin, Datura, Ephedra, and Glycyrrhizin. According to Phoenix Biotechnology, Oleandrin could help in the treatment of COVID-19. But later FDA denied its approval as a dietary supplement due to its associated poisoning manifested by nausea, vomiting, and abdominal pain followed by debility, drowsiness, hyperkalemia, and cardiotoxicity. Datura seeds were also recommended for treatment of COVID-19, but in high doses, it exhibits indications such as hallucinations, thirst, blurred vision, and difficulty in speaking or swallowing followed by tachycardia, hyperthermia, seizures, and respiratory arrest<sup>99</sup>.

**CONCLUSION:** Understanding the pathogenesis of CoV-2 and comparable information with previous viral infections propose opportunities to explore more treatment options. Phytochemical and herbal-based medicines are used and studied for their multi-mechanistic approaches against Co-V-2. Traditional medicinal systems provide immense knowledge and evidence for the efficacy of herbal-based preparations and phytoconstituents against

various viral infections. Several researchers have evaluated different extracts, herbal-formulations and identified phytoconstituents against different mechanisms of viral attachment, endocytosis, unpacking, transcription, translation, viral replication, assembly formation, etc. and underlying and associated proteins and enzymes of CoV-2. Promising efficacy was evident on the basis of *in-silico*, and *in-vitro* studies proposed further investigations of these compounds and formulations. Hence, thorough investigation and evidence discussed above recommend further evaluation and investigation of herbal-based medicines for their safe and effective use against CoV-2.

#### DECLARATION OF COMPETING INTEREST:

The authors declare that they have no competing interests.

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