Prospection of antiviral compounds from forest plants under ongoing SARS-CoV-2 pandemic

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Article Info

1. Introduction

The exponential spread of the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a serious global threat to human health. Severe acute respiratory syndrome (SARS) is a respiratory illness caused by SARS-CoV-2 (Drosten et al., 2003; Ksiazek et al., 2003; Peiris et al., 2003b; Poutanen et al., 2003). This febrile respiratory illness was initially described in early 2003 (Chan-Yeung and Yu, 2003; Donnelly et al., 2003; Lee et al., 2003; Peiris et al., 2003a; Tsang et al., 2003). The potential to cause life-threatening respiratory failure and rapid transmission placed SARS-CoV-2 in public health emergency of international concern (PHEIC) list (Al-Qahtani, 2020). In the last two decades, the world has faced three important outbreaks of very pathogenic CoVs, including the emergence of SARS-CoV between 2002 and 2003, Middle East Respiratory Syndrome (MERS-CoV) in the year 2012 till date and now COVID-19 is the 3rd deadliest coronavirus pandemic. The coronavirus disease 2019 (COVID-19) pandemic (previously known as 2019-nCoV) was first discovered in the city of Wuhan, China, at the end of December 2019. In a very short period, an outbreak of apparent idiopathic pneumonia had become the COVID-19 pandemic and countries worldwide are comprehensively trying to find preventative measures or cure against the acute resolving disease COVID-19. This pandemic situation warrants us to develop novel antiviral drugs immediately to control and prevent the spread of SARS-CoV-2.

India predominantly relied on plant-based medications under different domain names like Ayurveda, Siddha, Unani, etc. Though, the advent of allopathic medicines has cornered the prevalence of plant-based treatments, the current pandemic emphasizes the need for revisiting those plants and studying those using advanced tools and approaches. Technology interventions are the need-of-the-time to dissect the medicinal value of plants for identifying suitable phytochemicals that could serve as potential molecules in treating SARS-CoV-2. In this present scenario, exploration of plants with bioactive molecules of antiviral property for the development of novel drug is much needed. Several antiviral active compounds from medicinal plants against some notable viral pathogens including coronavirus (CoV), coxsackie virus (CV), dengue virus (DENV), entero virus 71 (EV71), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), influenza virus, measles virus (MV), and respiratory syncytial virus (RSV) have been discovered, however, nature and composition of those plants and their mode of actions are not available for drug development. The age-old antimalarial drug chloroquine (Cq), introduced in 1945 and its analogue hydroxychloroquine (Hcq) could be potent therapeutic agents against COVID-19 (Tripathy et al., 2020). Quinine an alkaloid obtained from the bark of Cinchona officinalis has been used in the treatment of malaria since the 1960s (Achan et al., 2011). In SARS-CoV-2, Hcq in combination with...
azithromycin found to be more effective in reducing the viral load (Gautreta et al., 2020). Similarly, glycyrrhizin, a saponin isolated from Glycyrrhiza glabra roots is reported to be effective against SARS-CoV by inhibiting viral replication (Cinatl et al., 2003b). As an RNA virus, 2019-nCoV may have the same functional proteins to process virus replication and assembly to human immuno-deficiency virus (HIV). As a result, HIV protease inhibitors may also be effective for 2019-nCov. Currently, the combination of lopinavir/ritonavir (LPV/R), which has been proven effective in SARS-CoV and MERS-CoV, has been recommended for treatment in 2019-nCoV. It is also reported that around 35 drugs and vaccines are under clinical trials for amelioration of COVID-19. AYUSH, Ministry of Health, GOI, New Delhi has recommended various traditional formulations for both preventive and symptomatic management of COVID-19 (Table 1) with add on interventions to conventional care from Ayurvedha, Siddha, Unani, and Homeopathy. There are around 25 plant species reported to have inhibitory activity on ACE, IL and other proteins such as Transmembrane protease, serine 2 (TMPRSS2); 3-chymotrypsin-like protease (3CLpro); spike, RNA-dependent RNA polymerase (RdRp), and papain like protease (PLpro) which would lead to develop drug for SARS-CoV-2. This review throws the state of knowledge on the antiviral compounds from medicinal plants under ongoing SARS-COV-2 pandemic.

**Table 1:** This table depicts the Indian medicinal plants and its usage provided by the AYUSH, Government of India as a therapeutic approach for COVID-19

| Indian medicinal plant | Form of extract | Trade name | Indian traditional medical practice | Preparation | Recommended usage | Effective against |
|-----------------------|-----------------|------------|------------------------------------|-------------|------------------|-----------------|
| **Preventive and prophylactic** |
| Tinospora cordifolia | Aqueous | Samshamanivati | Ayurveda | Samshamanivati 500 g with warm water | Twice a day for 15 days | Chronic fever |
| Andrographis paniculata | Aqueous | Nilavembukudineer | Siddha | Nilavembukudineer 60 ml decoction | Twice a day for 14 days | Fever and cold |
| Cydonia oblonga | Aqueous | Behidanaunnab | Unani | Behidana-3 g Unnab-5 Nos | Twice a day for 14 days | Antioxidant, immunomodulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity |
| Zizyphus jujube | Sapistan | | | | |
| Cordia myxa | | | | |
| Arsenicum album 30 | Tablet | Arsenicum album 30 | Homeopathy | Daily once in empty stomach for 3 days (should be presented after 1 month till the infection persist) | Effective against SARS-CoV-2, immunomodulator |

| **Symptomatic management for COVID-19** |
| Ayush-64 | Tablet | – | Ayurveda | – | 2 tablets twice a day | Respiratory infection |
| Agastya haritaki | Powder | Agasthya rasayanan | Ayurveda | 5 gm in warm water | Twice a day | Upper respiratory infection |
| Anathaila | Oil | Sesame oil | Ayurveda | – | 2 drops in each nostril daily morning | Respiratory infection |
| Adathodai manapagu | Aqueous | Adathodai manapagu | Siddha | – | 10 ml twice a day | Fever |
| Bryonia alba | Tablet | Bryonia | Homeopathy | – | – | Reducing lung inflammation |
Table 1: Homeopathic formulation

| Drug                         | Formulation       | Component | Dosage          | Ailment                            |
|------------------------------|-------------------|-----------|-----------------|-----------------------------------|
| Rhus toxicodendron           | Tablet            | Rhusox    |                 | Viral infection                    |
| Atropa belladonna            | Tablet            | Belladonna|                 | Asthma and chronic lung diseases. |
| Bignonia sempervirens        | Tablet            | Geisemium |                 | Asthma                            |
| Eupatorium perfoliatum       | Tablet            | Eupatorium|                 | Respiratory symptoms              |

Add on interventions to the conventional care

| Drug                         | Formulation       | Component | Dosage          | Ailment                            |
|------------------------------|-------------------|-----------|-----------------|-----------------------------------|
| Vishasura kudineer           | Tablet            | Polyherbal| Decoction 60 ml | Fever                             |
| Kabasura kudineer            | Tablet            | Polyherbal| Decoction 60 ml |                                    |

(Ref: AYUSH Ministry of Health Corona Advisory - D.O. No. S. 16030/18/2019 - NAM).

2. Genomic organization and virus structure

Coronavirus (COVs) are encased in a positive stranded RNA that comes into the coronavirinae subfamily. In addition, the genetic material is surrounded by nucleocapsid proteins in the nucleus and envelope that contain four proteins, such as spike proteins, envelope proteins, and membrane proteins. The genome of the CoVs range is long from 26 to 32 kilobase, which is perhaps the largest known RNA virus.

![Figure 1: Mode of action of coronavirus (CoV). (Source: Vellingiri et al., 2020).](image)

Among the viral structure, the S protein has a major role in binding the virus to the host receptor cells. S protein has two subunits which are the S1 receptor-binding subunit and S2 the membrane fusion subunit; where the earlier one attached itself to the ACE2 receptor of the human host cell and the S2 subunit internalizes and creates the membrane fusion among the viral subunit and the ACE2 receptors. This leads to the release of the viral RNA into the host cell and results into respiratory infection. Therefore, exploration of biologically active compounds to inhibit the SARS-CoV-2 spike protein into ACE2 receptor is the main priority (Figure 1).

Coronaviruses are present in a number of bat and bird species that are thought to serve as natural hosts. Molecular clock dating coronavirus analyzes suggest that the most recent common ancestor of these viruses was about 10,000 years ago. This relatively young age contrasts dramatically with the ancient evolutionary past of...
their supposed natural hosts, which started to diversify. It is found that the time for all coronaviruses common to the most recent ancestor is possibly much greater (millions of years) than the period previously inferred. In early 21st Century, severe acute respiratory coronavirus syndrome (SARS-CoV) and Middle East respiratory coronavirus syndrome (MERS-CoV) are the two major and highly infectious and pathogenic bat borne coronaviruses posed severe threats to humans.

3. Coronavirus cases in India

India’s coronavirus tally rose to 4.37 million with a single-day spike of 89,706 infections, while the death toll crossed the 73,890 mark with 1115 fresh fatalities, according to the Union Health Ministry data. The recoveries surged to 3.39 million pushing the recovery rate to 78 per cent. Meanwhile, Indian companies have asked the Russian Direct Investment Fund (RDIF) to provide the technical details of phase 1 and phase 2 clinical trials of Russia’s coronavirus vaccine, the world’s first registered vaccine against the infection. However, countries like India using dietary therapy and herbal medicines to prevent SARS-CoV-2 infections could be a complementary COVID-19 therapy, while drugs remain under development. Hence, the present review provides an insight into look at antiviral compounds from medicinal plants for the development of drugs for SARS-CoV-2 (Table 2).

Table 2: List of selected clinical trials for the amelioration of COVID-19 specific drugs and vaccines

| S.No. | Study | Drug | Status | Organization |
|-------|-------|------|--------|--------------|
| 1.    | Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19 | Sarilumab | Recruiting | Regeneron study site New York, United States |
| 2.    | Study to evaluate the safety and antiviral activity of remdesivir in participants with severe coronavirus disease (COVID-19) | Remdesivir | Recruiting | Hoag Memorial Hospital Presbyterian Newport Beach, California, United States: Stanford Hospital, Stanford, California, United States: Providence Regional Medical Centre Everett, Everett, Washington, United States |
| 3.    | Fingolimod in COVID-19 | Fingolimod 0.5 mg | Recruiting | Wan-Jin Chen Fuzhou, China |
| 4.    | The clinical study of carrimycin on treatment patients with COVID-19 | Carrimycin Lopinavir/ ritonavir tablets or arbidol or chloroquine phosphate | Not recruiting | - |
| 5.    | Efficacy and safety of corticosteroids in COVID-19 | Methylprednisolone | Recruiting | Hubei Province Hospital of Integrated Chinese and Western Medicine Wuhan, Hubei, China Yichang First People's Hospital Yuchang, Hubei, China Renmin Hospital of Wuhan University Wuhan, China |
| 6.    | Mild/moderate 2019 nCoV remdesivir | Remdesivir | Recruiting | Jin Yin-tan Hospital. Wu Han, Hubei, China |
| 7.    | Adaptive COVID-19 treatment trial | Remdesivir | Recruiting | National Institutes of Health Clinical Center, National Institute of Allergy and Infectious Disease Laboratory of Immunoregulation, Clinical Research Section. Bethesda, Maryland, United State University of Nebraska Medical Center Infectious Diseases, Omaha, Nebraska, United States, University of Texas Medical Center Infectious Disease. Galveston, Texas, United States Providence Sacred Heart Medical Center Spokane, Washington, United states |
|   | Severe 2019-nCoV remdesivir RCT | Remdesivir | Recruiting | Bin Cao Bejing, Benijing, China |
|---|---------------------------------|------------|------------|--------------------------------|
| 9 | Nitric oxide gas inhalation for severe acute respiratory syndrome in COVID-19. | Nitric oxide gas | Not yet recruiting | - |
| 10 | Efficacy and safety of IFN- '2' in the treatment of novel coronavirus patients | Recombinant human interferons - '1' | Not yet recruiting | - |
| 11 | Evaluating and comparing the safety and efficacy of ASC09/ritonavir and lopinavir/ritonavir for novel coronavirus infection | ASC09/ritonavir group Lopinavir/ritonavir group | Not yet recruiting | - |
| 12 | Safety and immunogenicity study of 2019-nCoV vaccine (MRNA-1273) to prevent SARS-CoV-2 infection | mRNA-1273 | Not yet recruiting | Kaiser Permanente Washington Health Research Institute Vaccines and Infectious Diseases |
| 13 | Glucocorticoid therapy for novel coronavirus critically Ill patients with severe acute respiratory failure | Methylprednisolone | Recruiting | Medical ICU, Peking Union Medical College Hospital Bejing, Beijing China |
| 14 | Lopinavir/ritonavir, ribavirin and IFN-beta combination for nCoV | Lopinavir/ritonavir Ribavirin Interferon beta-1B | Recruiting | University of Hong Kong, Queen Mary Hospital Hong Kong, Hong Kong |
| 15 | Efficacy of chloroquine and lopinavir / ritonavir in mild/general novel coronavirus (COVID-19) infections: A prospective, open-label, multicenter randomized controlled clinical study | Chloroquine Lopinavir / ritonavir | - | The Fifth Affiliated Hospital Sun Yat-Sen University |
| 16 | A study for the efficacy of hydroxychloroquine for mild and moderate COVID-19 infectious diseases | Hydroxychloroquine | - | The Second Affiliated Hospital of Chongqing Medical University |
| 17 | A prospective, randomized, open-label, parallel controlled trial for the preventive effect of hydroxychloroquine on medical personnel after exposure to COVID-19 | Hydroxychloroquine | - | Renmin Hospital of Wuhan University |
| 18 | The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19): multicenter randomized, open-label controlled trial | Carrimycin | - | Beijing Youan Hospital, Capital Medical University |
| 19 | A prospective clinical study for recombinant human interferon alpha infection in highly exposed medical staffs | Recombinant humaninterferon alpha 1b | - | Chinese PLA General Hospital |
| 20 | A pilot study of sildenafil in COVID-19 | Sildenafil citrate | Recruiting | Department and Institute of Infectious Disease, Wuhan Hubei, China |
| 21 | Comparison of lopinavir/ ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19) | Lopinavir/ ritonavir hydroxychloroquine sulfate | Recruiting | Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of Korea |
| Study Number | Study Title                                                                 | Intervention(s)                                      | Status                  | Location                                                                 |
|--------------|------------------------------------------------------------------------------|------------------------------------------------------|-------------------------|--------------------------------------------------------------------------|
| 22           | The efficacy and safety of thalidomide combined with low-dose hormones in the treatment of severe COVID-19 | Thalidomide                                         | Not yet recruiting      | -                                                                        |
| 23           | Various combination of protease inhibitors, oseltamivir, favipiravir, and chloroquine for treatment of COVID-19: A randomized control trial. | Oral                                                 | Not yet recruiting      | Subsai Kongsaengdao, Bangkok, Thailand                                   |
| 24           | Chloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting | Chloroquine                                          | Not yet recruiting      | -                                                                        |
| 25           | Favipiravir combined with tocilizumab in the treatment of coronavirus disease 2019 | Favipiravir combined with tocilizumab                | Recruiting              | Anhui Medical University Affiliated First Hospital, Hefei, Anhui, China |
| 26           | Trial treatment for COVID-19 in hospitalized adults                           | Remdesivir Lopinavir/ritonavir interferon beta-1A    | Not yet recruiting      | -                                                                        |
| 27           | Randomized controlled trial of losartan for patients with COVID-19 losartan requiring hospitalization | Losartan                                             | Not yet recruiting      | Hennepin Country Medical Center, Minneapolis, Minnesota, United States   |
| 28           | Evaluation of ganovo (danoprevir) combined with ritonavir in the treatment of novel coronavirus infection | Ganovo with ritonavir +/- Interferon                | Recruiting              | The Ninth Hospital of Nanchang Nanchang, Jiangxi, China                  |
| 29           | Eculizumab (soliris) in COVID-19 infected patients                            | Eculizumab                                           | Initiated               | -                                                                        |
| 30           | Expanded access remdesivir (RDV; GS-5734™)                                   | Remdesivir                                           | Initiated               | -                                                                        |
| 31           | Norwegian coronavirus disease 2019 study                                      | Hydroxychloroquine sulfate                           | Not yet recruiting      | -                                                                        |
| 32           | Post-exposure prophylaxis for SARS-coronavirus-2                             | Hydroxychloroquine                                   | Recruiting              | University of Minnesota Medical Center, Minneapolis, Minnesota, United States |
| 33           | The efficacy and the safety of pirfenidone capsules in the treatment of severe new coronavirus pneumonia (COVID-19) | Pirfenidone                                         | -                       | Third Xinzguya Hospital of Central South University                   |

Source: Vellingiri et al. (2020)
Many researchers have determined the inhibitory ability of various active compounds from natural resources. Compounds such as asiatic acid, andrographolide, apigenin, brazilein, brazilin, catechin, curcumin, gingerol, hesperidin, hesperetin, kaemferol, luteolin, myricetin, naringenin and quercetin against the target protein of SARS-CoV-2, particularly ACE2, TMPRSS2, RdRp, 3CLpro and PLpro through molecular docking studies by evaluating the binding energy between the active compound and the target proteins are well known (Laksmani et al., 2020). Laksmani et al. (2020) reported few active chemical compounds in medicinal plants showed excellent affinity towards target protein proved that they can be used as antivirals against SARS-CoV-2. The active compounds from Caesalpinia sappan L. such as brazilein and brazilin had an excellent affinity towards ACE2. Hesperidin from Citrus sp. to TMPRSS2 with most negative value of docking score and lower binding energy value than drugs such as arbidol, chloroquine, camostatmesylate, remdesivir and lopinavir that used as inhibitor agent to COVID-19 (Laksmani et al., 2020). Hence, the aforementioned medicinal plants could be a potential source of antivirals to develop drugs against SARS-CoV-2 through inhibiting ACE2, TMPRSS2, RdRp and protease (3CLpro and PLpro) that interfered the process of virus infection which causing pneumonia (Laksmani et al., 2020). Glycyrrhizin isolated from Glycyrrhiza glabra roots was found effective in preventing the SARS-CoV replication (Cinatl et al., 2003a); myricetin from Myrica rubra, scutellarein from Scutellaria baicalensis and Asplenium belangeri are known to inhibit the ATPase activity of SARS-CoV helicase nsP13 (Yu et al., 2020); amentoflavone, quercetin, luteolin and apigenin from Torreya nucifera (Ryu et al., 2010) and emodin, sinigrin and hesperetin extracted from Isatis indigotica (Lin et al., 2005) have inhibit 3CLpro function. Water extract of Houttuynia cordata has antiviral activity against SARS-CoV due to its inhibitory effect on 3C-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) of the virus; lycorine from Lycoris radiate (Li et al., 2005); 13 mannose-binding lectins identified to possess a robust anti-coronaviral activity (Keyaerts et al., 2007). Another lectin, agglutinin isolated from Galanthus nivalis, was effective against FCoV when administered in combination with a synthetic drug nelfinavir (Hsieh et al., 2010). Recently, resveratrol (trans-3, 5, 42-trihydroxystilbene) a natural stilbene derivative present in abundance in Vitis vinifera, Polygonum cuspidatum, and as Vaccinium macrocarpon showed inhibition of MERS-CoV infection (Lin et al., 2017).

Sivaraman and Pradeep (2020) and Vellingiri et al. (2020) had underlined the positive side of this plant-based concoction that keeps the infection levels at bay. Identification of the antiviral mechanisms from these natural agents has helped to understand how and where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus-host-specific interactions. It has been shown that natural plants (Table 3) contain antiviral activities to coronaviruses (McCutcheon et al., 1995) and the mechanism of action is to inhibit viral replication (Vlietinck and Vanden Berghe, 1991; Jassim and Naji, 2003). The Table 3 provides ethnobotanical details with respect to SARS - severe acute respiratory syndrome, MERS-Middle East respiratory syncytial virus, ARVI-Acute respiratory viral infections.

### Table 3: List of ethnobotanicals and their mode of action against CoV

| S. No. | Plant source | Mechanism of action | Target | Virus | References |
|--------|--------------|---------------------|--------|-------|------------|
| 1      | Acacia nilotica | Inhibition | -      | HIV-PR | Mishra et al., 2014 |
| 2      | Allium sativum | Proteolytic and hemagglutinating activity and viral replication | - | SARS | Keyaerts et al., 2004 |
| 3      | Andrographis paniculata | Suppression | NLRP3, Caspase-1, and IL-1 | SARS-CoV and likely SARS-CoV-2 | Liu et al., 2020a, 2020b |
| 4      | Boerhavia diffusa | Inhibition | ACE | - | Prathapan et al., 2013; Khan and Kumar, 2019 |
| 5      | Clerodendrum inerme | Inactivation | Ribosome | SARS-CoV-2 | Olivierir et al., 1996 |
| 6      | Cistus ternatea | Inhibition | Metalloproteinase inhibitor | ADAM17 | Maity et al., 2012 |
| 7      | Corydalis sativum | Inhibition | ACE | - | Pandey et al., 2011 |
| 8      | Cynara scolymus Cassia occidentalis Cascinum fernestrum | Inhibition | ACE | - | Prathapan et al., 2013; Khan and Kumar, 2019 |
| 9      | Embelia ribes | Inhibition | ACE | - | Prathapan et al., 2013; Khan and Kumar, 2019 |
| 10     | Eugenia jambolana | Inhibition | Protease | - | Otake et al., 1995 |
| 11     | Euphorbia granulata | Inhibition | - | HIV-1PR | Mishra et al., 2014 |
| 12     | Glycyrrhiza glabra | Inhibition of viral replication: Modulation of membrane fluidity | - | SARS; HIV-1 | Akamatsu et al., 1991; Cinatl et al., 2003a; Fiore et al., 2008 |
| 13     | Gymnema sylvestre | Inhibition of viral DNA synthesis | - | - | Vimalanathan et al., 2009; Arun et al., 2014 |
14. **Hyoscyamus niger** | Inhibition and Bronchodilator | Ca2+ | Gilani et al., 2008
15. **Ocimum lilimandscharicum** | Inhibition | - | HIV-1 | Thayilseema and Thyagarajan, 2016
16. **Ocimum sanctum** | Inhibition | - | HIV-1 | Rege and Chewdhary, 2014
17. **Panica granatuma** | Inhibition | ACE | - | Prathapan et al., 2013; Khan and Kumar, 2019
18. **Salacia oblonga** | Suppression | Angiotensin II, ATI Signal | - | He et al., 2011
19. **Sambucus ebulus** | Inhibition | - | Enveloped virus | Ganghu et al., 2015
20. **Solanum nigrum** | - | - | HIV-1 | Yu, 2004
21. **Sphaeranthus indicus** | Inhibition | - | Mouse coronavirus and Herpesvirus | Galani et al., 2010; Tiwari and Khosa, 2009; Vimalanathan et al., 2009
22. **Strobilanthes callosa** | Blocking | - | HCoV-NL63 | Tsai et al., 2020
23. **Strobilanthes casia** | Blocking | - | HCoV-NL63 | Tsai et al., 2020
24. **Vitex negundo** | Inhibition | - | HIV-1 | Nair, 2012
25. **Vitex trifolia** | Reduction | - | SARS-CoV | Liou et al., 2018

**Note:** HIV-IPR: Human Influenza Virus -1 Protease; SARS; Severe Acute Respiratory Syndrome; SARS-CoV: Severe Acute Respiratory Syndrome-Coronavirus; ACE-Angiotensin converting enzyme; HIV-1: Human Influenza Virus-1; gp120: Envelope Glycoprotein 120; CD4: Cluster of Differentiation; HCoV-NL63: Human coronavirus N62; RNA : Ribonucleic acid; MHV-A59: Mouse Hepatitis Virus-A59; Ca2+: Calcium ion; NLRP3: NLR Family Pyrin Domain Containing 3; ATI-Angiotensin 1; HCoV-NL63: Human Coronavirus-NL63.

### Table 4: Bioproducts against CoV

| Extracts or preparations | Test system | Test dose/concentration | Proposed mechanism | IC50 or EC50 value | References |
|--------------------------|-------------|--------------------------|--------------------|--------------------|------------|
| Lycoris radiata          | SARS-CoV    | $10^{-1} - 10^{-4}$ mg/ml| Undefined          | 2.4 ± 0.2 µg/ml | Li et al., 2005 |
| Artemisia lingua         | SARS-CoV    | $10^{-3} - 10^{-4}$ mg/ml| Undefined          | 34.5 ± 2.6 µg/ml| Li et al., 2005 |
| Pyrosis lingua           | SARS-CoV    | $10^{-1} - 10^{-4}$ mg/ml| Undefined          | 43.2 ± 14.1 µg/ml| Li et al., 2005 |
| Lindera aggregate        | SARS-CoV    | $10^{-1} - 10^{-4}$ mg/ml| Undefined          | 88.2 ± 7.7 µg/ml| Li et al., 2005 |
| Isatis indigotica        | SARS-CoV    | 1-500 µg/ml              | 3CL protease inhibition | - | Li et al., 2005 |
| Extract of Rheum officinale and Polygonum ulitflorum | SARS-CoV | 0-100 µg/ml | Inhibits the interaction of SARS-CoV S protein and ACE2. | 1 to 10 µg/ml | Ho, Wu, Chen, Li, and Hsiang, 2007 |
| Houttuynia cordata ethanolic extract | SARS-CoV | 0-400 µg/ml | 3CL protease and viral polymerase inhibition | - | Lau et al., 2008 |
| Herbal extracts (Gentiana scabra, Dioscorea batatas, Cassia tora, Taxillus chinensis, Cibotium barometz) | SARS-CoV | 25-200 µg/ml | 3CL protease inhibition | 39 µg/ml and 44 µg/ml (Two extracts of Cibotium barometz) | Wen et al., 2011 |
| Anthemis hyaline, Nigella sativa and Citrus sinensis extracts | Coronavirus infected HeLa-epithelial carinoembryonic antigen-related cell adhesion molecule la cells inoculated with MHV-A59 (Mouse hepatitis virus-A59) | 1/50 and 1/100 dilution of ethanolic extract (100 g/200 ml) | Increased IL-8 level, Significantly changed the expression of TRPA1, TRPC4, TRPM8, TRPM7, and TRPV4 genes | - | Ulashi et al., 2014 |
4. Natural products inhibiting virulence effect of CoV infection

Nature provides a vast library of chemicals to explore and develop drugs for treatment of various ailments including viral diseases (Denaro et al., 2019). Natural products and their derivatives are used in folk medicine will have always played a crucial role in drug development process against various diseases, which resulted in screening of such agents to combat emergent mutants of coronavirus (Ganjhu et al., 2015). There is a vast scope for herbal medicines in the view of nutraceuticals market (Williamson et al., 2020). Interestingly, the acceptability and, therefore, research on plant based drugs are growing on a daily basis. Some natural products have been found to exhibit their antiviral activity through the inhibition of viral replication (Moghadamtousi et al., 2015; Oliveira et al., 2017). Apart from plant derived compounds (Jardim et al., 2018), several marine natural products (Wang et al., 2014) as well as biotechnologically produced compounds (Neumann and Neumann Staubitz, 2010) are also reported for their antiviral properties against different viruses. Along this line, Nigella sativa demonstrated its inhibitory activity against hepatitis C virus (Oyero et al., 2016). General mechanism for antiviral activity of most of the natural products is inhibition of viral replication and some natural products (e.g., lycorine, homoharringtonine, silvestrol, ouabain, tylorhophorine and 7 methoxycryptopleurine) have interacted with important virulent viral proteins (Table 4). The natural compounds, procyanidin A2, procyanidin B1, and cinnamantin B1, isolated from Cinnamomi cortex inhibited SARS-CoV infection at 0-500 μM (Zhuang et al., 2009). On the other hand, tetra O galloyl beta D glucose, luteolin, and tetra O galloyl beta D glucose blocked the host cell entry of SARS-CoV at 0–10³ mol/l (Yi et al., 2004). In another study, bauchinim, neobavaisoflavone, isobavachalcone, 4’O methylbavachalcone, psoraladin, and corylifol isolated from Psoralea corylifolia inhibited papain like protease of SARS-CoV (Kim et al., 2014). Interestingly, psoraladin exhibited a strong protease inhibitory effect on SARS-CoV with an IC₅₀ value 4.2 μM, whereas emodin, rhein, and chrysin inhibited interaction of SARS-CoV (S) protein and ACE2 at 0-400 μM (Ho et al., 2007).

Table 5: Efficacy of secondary metabolites and their derivatives against CoV infection

| Compounds (Biological source) | Test system mechanism | Dose concentration | Proposed | IC₅₀ or EC₅₀ value | References |
|------------------------------|---------------------|--------------------|----------|------------------|------------|
| Aloe emodin (Isatis indigotica) | SARS-CoV | 1-100 μg/ml | 3CL protease inhibition | 8.3 μM | Lin et al., 2005 |
| Amentoflavone (Torreya nucifera) | SARS-CoV | 1-1000 μM | 3CL protease inhibition | 8.3 μM | Ryu et al., 2010 |
| Apigenin (Torreya nucifera) | SARS-CoV | 1-1000 μM | 3CL protease inhibition | 280.8 μM | Ryu et al., 2010 |
| Bavachinin (Psoralea corylifolia) | SARS-CoV | 1-150 μM | Inhibitors of papain like protease (PLpro). | 38.4 ± 2.4 μM | Kin et al., 2014 |
| Berbamine | HCoV-NL63 | 0-20 μM | Undefined | 1.48 μM | Kin et al., 2019 |
| Beta-sitosterol (Isatis indigotica) | SARS-CoV | 1-100 μg/ml | 3CL protease inhibition | 1210 μM | Lin et al., 2005 |
| Betulonic acid | SARS-CoV | 0-10 μM | Inhibition of replication | 0.63 μM | Wen et al., 2007 |
| Betulonic acid | SARS-CoV | 8-80 μM | 3CL protease inhibition | 10 μM | Wen et al., 2007 |
| Betulonic acid | SARS-CoV | 8-80 μM | 3CL protease inhibition | >100 μM | Wen et al., 2007 |
| Broussochalcone A (Broussonetia papyrifera) | 3-chymotrypsin -like and papain -like coronavirus cysteine proteases | 0-200 μM | Protease inhibition | - | Park et al., 2017 |
| (-) Catechingallate and (-) Gallocatechingallate | SARS-CoV | 0.001-1 μg/ml | Inhibition of nanoparticle-based RNA oligonucleotide | - | Roh, 2012 |
| Compound | Type | Concentration | Effect | Concentration | Reference |
|----------|------|---------------|--------|---------------|-----------|
| Cepharanthine | SARS-CoV | 0.5-10 µg/ml | Protease inhibition | 9.5 µg/ml | Zhang et al., 2005 |
| Cinanserin (1dpi) (Houttuynia cordata) | Murine CoV | 500-15.63 µg/ml | Undefined | 31.25 µg/ml | Cho et al., 2019 |
| Cinanserin (2dpi) (Houttuynia cordata) | Murine CoV | 15.63-500 µg/ml | Undefined | 62.50 µg/ml | Cho et al., 2019 |
| Cinnamantannin B1 (Cinnamomi cortex) | SARS-CoV | 0-500 µM | Inhibition of pseudovirus infection | 32.9 ± 3.9 µM | Zhuang et al., 2009 |
| Concanavalin A | - | - | Lose the haemagglutination properties of the virus envelope and cause a transient interference with infectivity | - | Greig and Bouillant, 1977 |
| Corylifol (Psoralea corylifolia) | SARS-CoV | 1-150 µM | Inhibitors of papain like protease (PLpro) | 32.3 ± 3.2 µM | Kim et al., 2014 |
| Curcumin | SARS-CoV | 8-80 µM | Inhibition of 3CL protease | 40 µM | Wen et al., 2007 |
| Dieckol (Ecklonia cava) | Porcine epidemic diarrhea CoV | 1-200 µM | Inhibition of viral replication | 14.6 ± 1.3 µM | Kwon et al., 2013 |
| Diplacone (Paulownia tomentosa) | SARS-CoV | 0-100 µM | Inhibition of papain like protease | 10.4 ± 0.16 µM | Chow et al., 2013 |
| 38,12-diacetoxyabieta-6,8,11,13-tetraene | SARS-CoV | 0-10 µM | Inhibition of replication | 1.57 µM | Wen et al., 2007 |
| 1-(4,5-Dihydroxy-3-hydroxymethylclope-2-enyl)-1H-1,2,4-triazole-3-carboxylic acid amide | SARS-CoV | - | Undefined | 21 µM | Cho et al., 2006 |
| 1-(4,5-Dihydroxy-3-hydroxymethylclope-2-enyl)-1H-1,2,4-triazole-3-carboxylic acid amide | SARS-CoV | - | Undefined | 47 µM | Cho et al., 2006 |
| Eckol (Ecklonia cava) | Porcine epidemic diarrhea CoV | 1-200 µM | Blockage of the binding of virus to cells | 22.5 ± 2.2 µM | Cho et al., 2013 |
| Emetine | HCoV-OC43, HCoV-NL63,MERS-CoV and MHV-A59 | 0-5 µM | Inhibited RNA,DNA and Protein synthesis | 0.30,1.43, 0.34 and 0.12 µM | Shen et al., 2019 |
| Emodin (1,3,8-trihydroxy-6-methylanthraquinone) | SARS-CoV | 0-400 µM | Inhibited interaction of SARS-CoV (S) protein and ACE2 | 200 µM | Ho et al., 2007 |
| Fangchinoline | HCoV-OC43-infected MRC-5 human lung cells | 2-20 µM | Undefined | 1.01 ± 0.07 µM | Kim et al., 2019 |
| Ferruginol | SARS-CoV | 0-10 µM | Inhibition of replication | 1.39 µM | Wen et al., 2007 |
| 6-geranyl-4',5,7-trihydroxy-3',5'-dimethoxy-flavanone (Paulownia tomentosa) | SARS-CoV | 0-10 µM | Inhibition of replication | 13.9 ± 0.18 µM | Cho et al., 2013 |
| Halituna (Halimeda tuna) | Murine coronavirus A59 | - | Undefined | - | Koehn et al., 1991 |
5. Conclusion

COVID-19 a newly emerged upper respiratory tract viral respiratory disease caused by the coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identified from China, in December 2019, spreads rapidly across worldwide. A novel coronavirus disease (COVID-19) is zoonotic and also transmitted from human-to-human rapidly leading to pandemic responsible for the current global health crisis. COVID-19 spreads over 221 countries and territories around the world with total confirmed cases of 130 million and 2.84 million deaths. While drugs remain under development, using conventional medicines along dietary therapy are recommended by Ayush, Govt. of India to prevent and boost immunity to tackle SARS-CoV-2 infections. Exploration of antiviral compounds from medicinal plants to develop drugs for SARS-CoV-2 is highly warranted.

6. Solution strategy to combat COVID-19

The spectrum of symptoms associated with COVID-19 ranges from difficulties in breathing and other respiratory conditions to critical conditions including kidney failure, heart attack and sometimes even death and, therefore, the following strategies have been recommended to avoid spread of COVID-19.

- Avoiding international and domestic travels to spread the infection from severely affected areas/countries.
- Individuals are likely to be infected by others who have been infected with the virus. The disease can spread from person-to-person via small droplets from nose or mouth when a person with COVID-19 coughs or exhales; these particles in the air, settle on surfaces in the environment further infecting people who breathe these particles or touch these places and then touch their body parts, and hence 6 feet physical distance is recommended (WHO, 2020).
- Reports suggest that older persons and persons with pre-existing medical conditions (such as high blood pressure, heart disease, lung disease, cancer or diabetes) appear to develop serious illness more often than others, and hence co-morbid patients must be treated with utmost care.
- Also, it has been reported that some of the Asian populations are more susceptible to acquire this COVID-19 infection when compared to the other races populations, needs special attention.
- National Institute of Health (NIH) has mentioned that SARS-CoV-2 could survive for up to 3 h maximum as aerosols to a maximum of three days on surfaces.
- Slowing the spread of the COVID-19 cases will significantly reduce the strain on the healthcare system of the country by limiting the number of people who are severely sick by COVID-19 and need hospital care.
- So, it is time for all the citizens to join hands together to fight against coronavirus by practicing self-hygiene and physical distancing.
- WHO is coordinating efforts to develop medicines to prevent and treat COVID-19.
- India as a front runner developed an indigenous COVID vaccine COVAXIN along with Covishield (the Oxford-AstraZeneca vaccine) and started vaccination campaign on 16th January, 2021. As of 31st March 2021, India’s vaccination programme has given 65.1 million doses of vaccine with 9.3 million Indians having had two doses, and targeted to vaccinate 30 crores in near future.

7. Dietary therapy and herbal medicine could be used against COVID-19 in the following four ways

- Diet or supplement for infection prevention and immunity strengthening.
- Application as antiviral agent on masks.
- Air disinfection agent to stop aerosol transmission of the virus.
- Surface sanitizing agent to afford a disinfected environment.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.
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