

Relevance of Fast Track Integrative Approaches for the Control of COVID-19

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Abstract

The current global pandemic of COVID-19 has spread over 212 countries with marked morbidity and substantial mortality. This has resulted in colossal burden on the worldwide healthcare system. Globally the management of this new disease is primarily supportive and resuscitative. Vaccine and anti-COVID-19 drugs are still under development. Oriental medicine of India and China and the medicinal plants offer a potential for a fast track development of phytopharmaceuticals. In the present overview we have shortlisted the following Indian medicinal plants, based on their traditional usage and scientific rationale: *Phyllanthus amarus* Schum and Thonn., *Berberis aristata* DC., *Swertia chirata* and *Andrographis paniculata* (Burm. f.). These medicinal plants and the phytoactives can be rapidly evaluated for anti-COVID-19 activity through reverse pharmacology.

Keywords: COVID-19, reverse pharmacology, medicinal plants, antiviral activity, phytopharmaceuticals

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Corona Virus Disease-19 (COVID-19) is a global pandemic that has changed the world as we know it in a short period of 5 months. As of 12, May 2020, the global estimate for COVID-19 cases is 4.1 million cases with more than 280,000 deaths, and it is unclear yet whether we have reached the peak of infection world over.¹ This has compelled scientists from diverse medical systems and allied disciplines to investigate modalities to control, prevent, treat, and alleviate the symptoms of this viral disease.²⁻⁵ The multitude of approaches adopted span from public health and epidemiological strategies dependent on non-pharmacological measures, including social distanc-

ing, contact tracing, testing, quarantine, and isolation, to the usage of antiviral drugs, vaccines under trial and immunity-enhancing interventional approaches. An approach that does deserve attention is fast-tracking the research and development of anti-COVID-19 phytopharmaceuticals that draw upon insights and experiential evidence from traditional medicine through reverse pharmacology. Given the urgency of the situation, repositioning of both modern and traditional medicine drugs, compassionate use of experimental medicines, and application of remedies based on traditional medicine have been advocated.⁶⁻⁸

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In India, the pluralistic health care system, despite its challenges, offers a wide potential for an organized multisystem research and development. Over the last few decades, integrative approaches such as Ayurvedic Pharmacoepidemiology, Observational Therapeutics, and Reverse Pharmacology have drawn on insights from traditional medicine while incorporating the tools and technology of modern science, opening up the path for an integration drawing from the best of diverse systems of the healing arts.⁹ One offshoot of this endeavour was the establishment of the Advanced Centre of Reverse Pharmacology in Traditional Medicine at the Medical Research Centre of Kasturba Health Society in 2007. Recently a task force employing a similar approach has been constituted between the ministry of AYUSH and CSIR by the Government of India. On March 17th, the following plants with their phytoactives were suggested by one of us (ABV) to research leaders and Government Research Councils for paraclinical and subsequent clinical studies in young patients with mild or moderate disease.

We have carried out a relevant literature search and have shortlisted the following Indian plants, based on their traditional usage and scientific rationale: (1) *Phyllanthus amarus* Schum. and Thonn.: specific plant strain with adequate concentration of geraniin, (2) *Berberis aristata* DC.: with a high concentration of berberine, (3) *Swertia chirata* (Roxb. Ex Flem.) with an adequate concentrations of iridoid glycosides and (4) *Andrographis paniculata* (Burm. f.): with adequate concentration of andrographolides

***Phyllanthus amarus* Schum. and Thonn.**

In Ayurveda the plant is known as *Bhumyamalaki*. Various *Phyllanthus* species *P. amarus* Schum. And Thonn., *P. fraternus* Web., *P. maduraspatensis* Linn., *P. simplex* Retz., *P. urinaria* Linn. are being termed as "*Bhumyamalaki*."¹⁰ Its Ayurvedic properties and multiple uses are well described and detailed.¹¹

P. amarus has been considered as an important plant with antiviral activity since Blumberg and colleagues had shown its antiviral activity in hepatitis B.¹² Our group had not confirmed the clearance of hepatitis B virus in the carriers¹³ which could be due to lower or no concentration of the important phytoactive/s of the plant. Recently *P. amarus* has been shown to act at multiple targets in HIV affecting different steps in the HIV life cycle.¹⁴ The alcoholic extract of the plant contains corilagin and geraniin in 2.28 and 1.10%, respectively. Corilagin and geraniin were found to have good antiviral activity against HIV-1 strain, even rep-

lication of HIV-1 was inhibited at low concentration. Hydroalcoholic extract of *P. amarus* was also active at a very low concentration which might be due to synergy of both gallotannins and other components like geraniin in the extract.

Geranii herba (*G. herba*), a perennial plant from Asia contains corilagin and geraniin. Extract of *G. herba* has been studied in the influenza virus and it was found that *G. herba* worked through inhibition of neuraminidase and increased the survival of MDCK cells infected with influenza viruses.¹⁵ It is of interest to note that influenza neuraminidase inhibitors like oseltamivir have been widely used for 2019-nCoV for suspected cases in hospitals in China.

Antiviral activity of *Phyllanthus amarus* has also been shown to suppress viral oncogenesis as the plant extract has shown suppression of Friend murine leukemia virus (FMuLV)-induced erythroleukemia in BALB/c mice.¹⁶

***Berberis aristata* DC.**

This is called Daruhaldi in the Indian system of medicine. *Daruharidra* is used in multiple conditions like *Vrana* (wound healing), *Meha* (diabetes), *Karnanetraakshiroga* (ear, eyes, oral diseases), *Shopha* (inflammation), *Visarpa* (herpes infection) and *Vishahara* (antitoxin).¹⁷

The most studied molecule of *Berberis aristata* and that of *Coptis chinensis* is Berberine. Berberine as well as berberine derivatives have shown anti-neuraminidase activity for influenza virus.¹⁸ Some of these showed stronger antiviral activity as compared not only to the pure berberine but also to the standard drug Oseltamivir.¹⁸ In one study using berberine isolated from *Coptis chinensis* it was seen in an *in-vitro* study that Berberine inhibited growth of influenza virus in A549 cells at 20 µg/ml concentration. Yu-Qi Yan et al. reported antiviral effect of berberine in influenza infested mice.¹⁹ The H1N1 influenza virus-induced weight loss was inhibited and there was a remarkable reduction in pulmonary oedema, inflammation and necrosis of the infected animals.¹⁹ Besides its antiviral activity berberine is a powerful anti-inflammatory phytomolecule.^{20,21} *Berberis aristata* treatment in the arthritis model of animals has produced a significant reduction ($P < 0.01$) in serum inflammatory cytokine levels. Protein expression of IL-1 β , IL-6, TNF-R1, and COX-2, was found to be reduced in stimulated macrophages, whereas anti-inflammatory cytokine, IL-10, was up regulated in peritoneal macrophages.²¹

Swertia chirata (Roxb. Ex Flem.)

Swertia chirata: Kirattikta is used in Pittasranut (bleeding disorder), Shopha (inflammation), Kasa (cough), Trushna (thirst), Jwara (fever), Krimi (worm infestation), Meha (diabetes), Shwasa (dyspnoea), Daha (burning sensation), Vrana (faster wound healing).²²

Swertia chirata has a wide range of bioactive compounds such as alkaloids, flavonoids, iridoids, lignans, secoiridoids, and terpenoids. *S. chirata* extract has shown antiviral activity against Herpes Virus type-1.²³ It inhibited the viral plaque formation and viral dissemination. The plant extract had the potential to have antiviral activity as compared to acyclovir drug-treated virus control. A 50% hydroalcoholic extract of *S. Chirata* is found to inhibit secretion of Hepatitis B surface antigen, and Hepatitis B e antigen, further 30 compounds from this extract were isolated to check individual efficacy. Some of them were found to inhibit HBV replication. One of the compounds, 1-hydroxy-3,7-dimethoxyxanthone, had an IC₅₀ value of 0.16 ± 0.021mM.²⁴

Andrographis paniculata (Burn. f.) Nees

It is known as *kalmegh* or *bhunimba* in Ayurvedic material medica. It is bitter in taste, hot in potency and light for digestion. As per Ayurveda it pacifies kapha and pitta doshas. It is used in *gulma* (abdominal swelling / distention), *gar* (internal toxins) *hridroga* (cardiac problems), *kushtha* (skin diseases), *shopha* (inflammation), *udar* (ascites). It is used in loss of appetite, liver and spleen disorder especially jaundice, and worm infestation.^{25,26}

Whole plant of this herb is used for the preparation of various single herb formulations like powder, decoction and juice. Dose of dried powder of whole plant is 1 to 3 grams. While for decoction and juice it is 20 to 30ml and 5 to 10ml respectively.²⁶

Seasonal outbreaks of influenza fever with associated pneumonia are well-known causes for severe morbidity and high mortality. H1N1 viral infection is known to cause fatal pneumonia because of acute respiratory syndrome.²⁷ *A. paniculata* and its bioactive molecules have shown anti-viral, anti-inflammatory and immunomodulatory activities in *in-vitro*, *in-vivo* and in clinical pharmacological studies.²⁸⁻³⁰

Conclusions

The global challenge of COVID-19 is formidable.³¹ There is a need to think 'out-of-the-box' for fast track approaches to control the scourge. China and India do have a rich history and a live heritage of Traditional Chinese Medicine and Ayurveda respectively. A re-

view of experience, experimental data and clinical studies have identified four plants for the development of phytopharmaceuticals with standardization of photoactive/s and reverse pharmacology trans-discipline. The four plants are *P. amarus*, *B. aristata*, *S. chirata* and *A. paniculata*. One of the four can be taken up for clinical trial prioritized on the basis of emergent paraclinical evidence. An expert team consisting of reverse phamcologist/s, Ayurvedic experts, phytochemists and virologists will have to closely collaborate with the front-line experts in infectious diseases dealing with COVID-19 cases. It is desirable that industrial and academic R&D teams work in synergy.

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