

## Ayurveda rasayana in prophylaxis of COVID-19

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Respiratory viral infections such as SARS-CoV-2 affect immune homeostasis by altering the immune regulatory network leading to decreased responsiveness, changes in lymphocyte subpopulations and decreased macrophage function<sup>1</sup>. Clinically, the immune response induced by SARS-CoV-2 infection occurs in two phases: the first immune defence-based protective phase and the second inflammation-driven damaging phase<sup>2</sup>. The first immune defence-based protective phase is characterized by recruitment of antibody-secreting cells, follicular helper T-cells, activated CD4 and CD8 T-cells and immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies that bind to SARS-CoV-2 (ref. 3). The second phase leads to uncontrolled cytokine release causing cytokine release syndrome (CRS), or 'cytokine storm' characterized by increased IL-2, IL-7, granulocyte colony stimulating factor, IFN-gamma and TNF-alpha<sup>4</sup>. CRS damages tissues of the lungs, kidney and heart leading to rapid multi-organ failure. The deaths from COVID-19 are due to massive alveolar damage leading to acute respiratory distress syndrome (ARDS) that culminates in respiratory failure. Restoration of Th1/Th-2 cytokine balance is one of the mechanisms of establishing immune homeostasis<sup>5,6</sup>.

Globally, it is suspected that there is a pool of covert COVID-19 cases of asymptomatic patients<sup>7</sup>. These cases pose a threat for widespread transmission of the disease. In the absence of a vaccine, this will require therapeutic strategies targeting pre- and post-exposure prophylaxis. During the incubation and non-severe stages (protective phase), a specific balanced Th1/Th2 response characterized by activated CD4+ and CD8+ responses leading to neutralizing antibodies against SARS-CoV-2 is required to eliminate the virus and to prevent disease progression to severe stages<sup>3</sup>. Modulation of immune responses is known to be useful in reducing disease aggravation and mortality rate<sup>8</sup>.

Chloroquine (CQ) and its less toxic derivative hydroxychloroquine (HCQ)

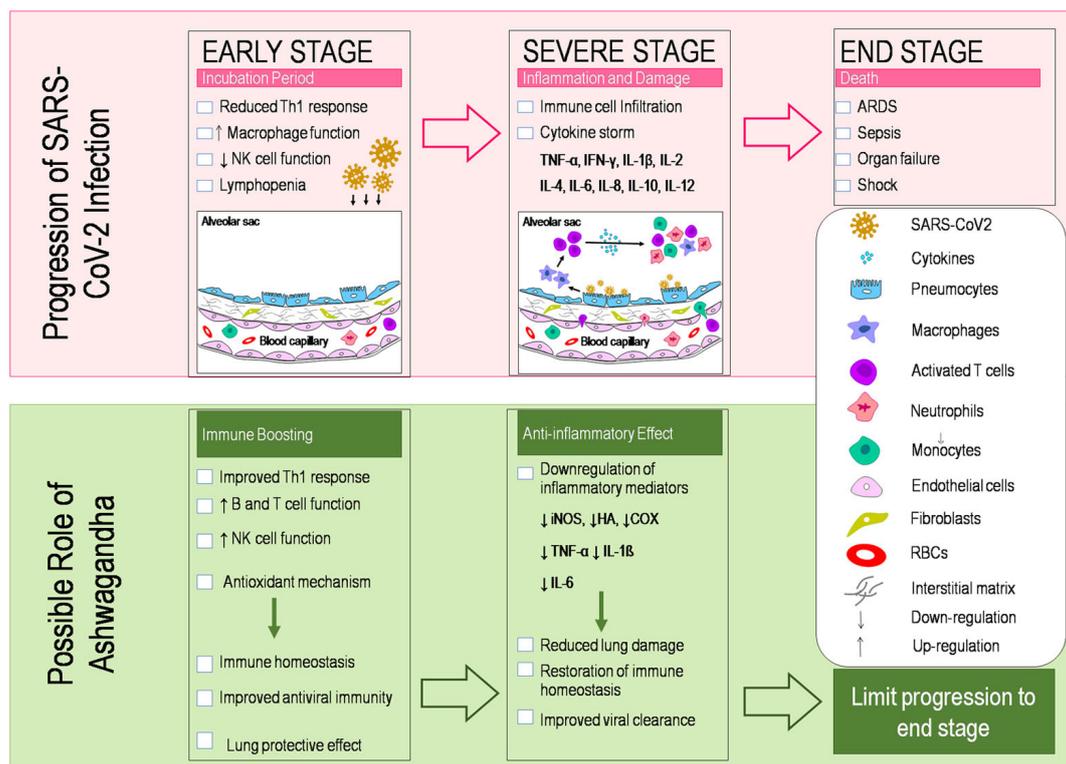
are used as treatment for malaria, chikungunya, rheumatoid arthritis (RA), lupus and some other autoimmune disorders<sup>9</sup>. A randomized controlled trial in Indian patients of chikungunya has concluded that HCQ is no better than an anti-inflammatory analgesic<sup>10</sup>. In current situation, HCQ is considered as a candidate for COVID-19 treatment due to its immunomodulatory and antiviral effects<sup>11,12</sup>. However, data to support the use of HCQ and CQ for COVID-19 seem to be limited and inconclusive<sup>13</sup>. At present, CQ and HCQ are under investigation in a multicentric SOLIDARITY trial initiated by WHO<sup>14</sup>. Meanwhile, the National Taskforce on COVID-19 constituted by the Indian Council of Medical Research, New Delhi, has recommended a protocol for the use of HCQ for prophylaxis of SARS-CoV-2 infection for protection of high-risk individuals. The Drug Control General of India has approved this protocol for restricted use under emergency situation<sup>15</sup>.

Scientific evidence based on our research spanning over 25 years, indicates that Ayurveda rasayana such as Ashwagandha (*Withania somnifera* L. Dunal; WS), can be a potential candidate for management of COVID-19. Ashwagandha can offer multi-target effects in inflammatory conditions by restoring immune homeostasis<sup>16</sup>. We have demonstrated clinical success with Ashwagandha containing Ayurvedic formulations to treat both acute and chronic rheumatoid arthritis in well-designed clinical trials<sup>17-19</sup>. In a randomized controlled trial, a formulation containing Ashwagandha was shown to have efficacy equivalent to HCQ with better safety in treating RA<sup>20</sup>. In the treatment of COVID-19, broad immunosuppression leading to anti-inflammatory effect may delay virus clearance by impairing induction of antiviral immunity<sup>21</sup>. In such a scenario, Ashwagandha can be beneficial as it promotes immune homeostasis rather than unidirectional immune suppression or immune stimulation.

We have evaluated Ashwagandha in various experimental conditions, including those of infection, inflammation,

cancer and arthritis<sup>22-29</sup>. A selective Th-1 upregulating activity of WS was demonstrated in mouse models<sup>30</sup>. In infection models, pre- and co-administration of WS extract with DPT (diphtheria pertussis tetanus) vaccine resulted in efficient protective immune responses against lethal challenge of diphtheria and pertussis toxins. In a study, prophylactic administration of WS was found to modulate Listeria-induced suppression by inducing myeloid progenitors in the bone marrow and increased IFN-gamma levels<sup>31</sup>. In another study, supplementation of infectious bursal disease virus (IBDV)-infected chicken with WS root powder alleviated virus-induced stress and immunological alterations, and reduced viral persistence in the host<sup>32</sup>. WS as an adjuvant in conjunction with anti-tuberculosis (TB) drugs used as directly observed treatment, short-course (DOTS) showed a favourable effect on symptoms and immunological parameters in patients with pulmonary TB<sup>33</sup>. Vaccine adjuvant activity of WS was attributed to specific ratios and combinations of withanolides<sup>34</sup>. In another experiment, immunorestorative activity of WS was reported in an anaphylaxis model<sup>17</sup>. In tumour models, WS-derived fractions showed significant immunomodulatory activity by counteracting the myelosuppressive effects of chemotherapy and inducing an improved immune response leading to reduction of tumour size<sup>18</sup>. In comparative studies of Ashwagandha and Chinese Ginseng in animal models, superior activity of WS in terms of immunomodulation was observed<sup>35</sup>.

We suggest that Ashwagandha would be an effective agent in the management of COVID-19 through modulation of host Th-1/Th-2 immunity. WS may be beneficial in inducing anti-viral immunity (owing to increased IFN- $\gamma$  responses) and optimum anti-inflammatory activities (downregulation of IL-1, IL-6, TNF- $\alpha$  and other inflammatory mediators) which are the key targets relevant to COVID-19 (Figure 1). In addition, other Ayurveda rasayana such as *Tinospora cordifolia* (Guduchi), *Asparagus racemosus* (Shatavari), *Phyllanthus*



**Figure 1.** Possible role and immune targets of ashwagandha in prophylaxis of COVID-19. (Top panel) The phases and mediators of immune response elicited by SARS-CoV-2; the early stage (immune-protective phase), severe stage (inflammation/damage phase) and end stage. (Bottom panel) The possible activities of WS on immune mediators during different phases of immune response to SARS-CoV-2.

*emblica* (Amalaki), etc. also have immunomodulatory properties, and may have the potential to bolster health and immunity of the community in the fight against SARS-CoV-2 infection<sup>36</sup>.

China has boldly adopted integrative approach involving modern medicine and traditional Chinese medicine (TCM)<sup>37</sup>. Systematic efforts for investigating TCM formulations for COVID-19 are underway in China<sup>38</sup>. Most of the studies follow integrative management employing a blend of TCM and conventional regimens for diverse clinical end-points like coronavirus pneumonia, pulmonary fibrosis, pulmonary function, and improvement in quality of life and emotional status. The earlier experiences of prevention trials for SARS and H1N1 have helped the authorities to plan TCM-based COVID-19 prevention programmes in 23 provinces of China<sup>39</sup>. Over 60,000 cases have been treated with TCM till February 2020. The reported benefits of TCM include reduction in recovery time, shortened hospital stays, improvement in clinical cure rate and the disease prevention observed in CT scans.

One of the important advantages is limiting transformation of mild to moderate cases into the critical stage and thereby enhancing overall prognosis<sup>40,41</sup>. In the current Indian scenario, lessons from China are important for planning similar fast-track clinical trials on simple Ayurvedic medicines such as Ashwagandha, Guduchi, Yashtimadhu and Amalaki for prophylaxis and management of SARS-CoV-2 infection.

It is possible to save millions of lives from SARS-CoV-2 infection by enhancing host defence. We hypothesize that efficacy and safety of current therapeutics may be enhanced by reducing intensity of CRS responsible for ARDS. India has an opportunity for a global leadership in developing evidence-based prophylactic and therapeutic strategies on the basis of Ayurveda. The war against COVID-19 requires transdisciplinary approach with the involvement of researchers from medicine, science, technology and social sciences. For this to happen, we need active research collaboration among the Ministry of AYUSH, Ministry of Health (ICMR institutions),

Ministry of Science and Technology (CSIR, DBT, DST institutions) and Ministry of Human Resource Development (UGC, AICTE and ICSSR), Government of India, to fight the war against COVID-19. It is worth noting that National Science and Engineering Academies from India have already taken steps to establish a joint National Task Force for S&T response to COVID-19.

There could be good ideas and successful experiences of the AYUSH sector, which can help in the national effort against COVID-19. Scientific exploration of AYUSH may happen in parallel; however, the current priority is protecting people. The Prime Minister Narendra Modi during interaction with AYUSH stakeholders has rightly advised them to avoid tall claims without sufficient scientific evidence. He has also appealed for the involvement of AYUSH sector in the war against COVID-19. Subsequently, the National Task Force on COVID-19 is likely to involve the Ministry of AYUSH along with ICMR, CSIR, DBT and DST. This is a welcome step. We suggest that under current exceptional circumstances,

interdisciplinary research on evidence-based Ayurveda interventions should be prioritized with an open mind for prophylaxis and add-on treatment of SARS-CoV-2 infection.

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