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Comprehensive Review of the Therapeutic Potential of AYUSH-64 against COVID-19

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Abstract

The global pandemic of the Corona virus disease (COVID-19) has caused widespread morbidity and mortality globally. The complicated pathophysiology of COVID-19 and lack of a single therapy have made management a significant issue. Through comprehensive pharmacological, toxicological, and clinical research, AYUSH-64, a poly-herbal formulation developed by CCRAS, ministry of AYUSH, government of India, has demonstrated both its safety and effectiveness in treating infective febrile illnesses like malaria and influenza. Four components in AYUSH-64 include antiviral, immunomodulatory, anti-inflammatory, antipyretic, and anti-inflammatory properties. In COVID-19, it stops the inflammatory responses that lead to substantial morbidity. The government of India has also included AYUSH-64 in the National COVID management protocol based on Ayurveda and Yoga for asymptomatic and mild cases of COVID-19. The study summarizes the therapeutic potential of AYUSH-64 on the basis of clinical trials conducted in India on COVID-19.

Keywords: Ayurveda • COVID-19 • AYUSH-64 • Ribonucleic Acid (RNA) • Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Introduction

The late-2019 outbreak of Coronavirus disease (now known as COVID-19) in Wuhan, China triggered a global public health emergency that now affects more than 200 countries worldwide. Coronavirus is a positive-sense Ribonucleic Acid (RNA) with crown-like spikes from the Coronaviridae family. Over the last two decades, pandemics caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) resulted in 10% and 37% mortality rates, respectively [1]. A new Coronavirus of probable bat origin caused an outbreak of human pulmonary disease in Wuhan, China, in December 2019, which quickly spread throughout the world [2]. The World Health Organisation (WHO) initially referred to the causative agent as 2019-novel Coronavirus (2019-nCoV). According to the International Committee of Coronavirus Study Group (ICCSG), the virus named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) shares 82.30% of its RNA genome and pathogenesis (host) with SARS Coronavirus (SARS-CoV) [3]. The disease was finally termed Coronavirus disease 2019 (COVID-19) (WHO, 2020). On January 30, 2020, WHO officially declared the COVID-19 epidemic a public health emergency of international concern, and the outbreak was confirmed as a pandemic on March 11, 2020. SARS-CoV and SARS-CoV-2 share a similar pathogenesis (host) due to genome similarities.

The government of India's Ministry of AYUSH (MoA) has undertaken a number of R and D and public health projects to examine how AYUSH systems might be used to lessen the effects of the COVID-19 pandemic. To conduct research on COVID-19 using various AYUSH systems, numerous institutions under the ministry of AYUSH have partnered with renowned medical and scientific companies around the nation. In order to handle different aspects of clinical and experimental research through AYUSH interventions, the MoA established an inter-disciplinary AYUSH R and D Task Force made up of scientists, pulmonologists, epidemiologists, pharmacologists, etc. from prestigious organisations and research institutions. A series of self-care recommendations for preventive health measures was also suggested by the ministry of AYUSH, with a focus on respiratory health and boosting overall immunity. To enable uniform clinical management, the ministry of AYUSH further released the national clinical management protocol based on Ayurveda and Yoga for management of COVID-19 [4]. The protocol's recommended management practises are based on intermediate trends and findings from the AYUSH COVID-19 investigations as well as published data on the security and possible advantages of AYUSH interventions.

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Literature Review

About AYUSH-64

The central council for research in ayurvedic sciences, India's apex organisation for Ayurvedic research and development under the ministry of AYUSH, government of India, developed AYUSH-64, a poly-herbal compound. Saptaparna (*Alstonia scholaris* R. Br.) bark aqueous extract 100 mg, Katuki (*Picrorhiza kurroa* Royle ex. Benth) root extract 100 mg, Kiratatikta (*Swertia Chirata* Pexbex. Karst) whole-plant extracts 100 mg, and Kuberaksha (*Caesalpinia crista* L.) seed powder 200 mg are the four ingredients [5]. All four AYUSH-64 components have a bitter flavour, making them amapachak (able to digest the bitterness). Ama or food that has not been digested), and hence they behave like Jvaraghna (antipyretic). The combined effects of these herbs include jwarahara (which can relieve fever), sannipata jwarahara (which can relieve intermittent fevers), krimihara (which is wormicidal), jantuhara (which is anthelmintic/antimicrobial/antiviral), and shothahara (which is anti-inflammatory). This compound is effective against conditions like influenza-like illnesses, which have the symptoms of cough, cold, headache, and fever. According to reports, a number of the drug's constituents have pharmacological properties that include antimalarial, antiviral, anti-inflammatory, and immunomodulatory effects. Studies suggests that AYUSH-64 is a safe and non-toxic formulation in a dose of 500 mg/kg body weight for 12 weeks in experimental studies [6,7] At the department of molecular virology laboratory, possible antiviral efficacy of Chirakin (marketed as AYUSH-64 by Zandu) against the Chikungunya virus was examined. In order to assess the effectiveness of the chemical in terms of activity index and selectivity index in a protection experiment, Vero cells were infected with the Chikungunya Virus (CHIKV) and treated with an optimal concentration of Chirakin (25 mg/mL) at the Rajiv Gandhi centre for biotechnology in Thiruvananthapuram, testing for plaque prevention and reduction. Plaque test in vero cells was used to measure the reduction in viral yield in cells treated with chirakin. In this study, chirakin has antiviral action against the chikungunya virus. In protection testing, it was found to be more active than ribavirin, although both drugs perform almost equally well in plaque reduction assays (CK Katiyar technical note on chirakin tablet unpublished report) (Table 1).

S. No.	Plant name	Activity
1	Saptaparna (*Alstonia scholaris* R. Br.)	a. Anti-HSW and anti-adenovirus activity of indole alkaloids from leaves of *Alstonia scholaris*, with significant inhibitory activity against Herpes Simplex Virus (HSV) and adenovirus (L Zhang, et al.).
		b. *In vitro* tests, alkaloids exhibited inhibition of inflammatory mediators (COX-1, COX-2 and 5-LOX), which is accordant with results on animal model (JH. Shang, et al.).
		c. Potent antiplasmodial activity against *P. falciparum* (C Christina, et al.).
		d. Its strong schizonticidal activity prevents malarial fever (S Singh, et al.).
2	Kiratatikta (*Swertia Chirata* Pexbex. Karst)	a. The drug has a promising effect due to its antipyretic and antimalarial properties (Bhargava, 2009). Anti-protozoal activity: A MeOH extract of Swertia chirata found to inhibit the catalytic activity of Leishmania donovani topoisomerase I was fractionated to yield three secoiridoid glycosides: (i) Amarogentin, (ii) Amaroswerin, and (iii) Sweroside. Amarogentin is an effective inhibitor of leishmania type I DNA topoisomerase that works by interacting with the enzyme and preventing the formation of binary complexes.
		b. Inhibits the expression of viral protein R (an attractive target for HIV disease) in HeLa cells harbouring the TREx plasmid encoding full-length Vpr (TREx-HeLa-Vpr cells) (SY Woo, et al.).
		c. HSV-1 infection, plaque formation, and viral dissemination were all reduced by more than 70%. (H Verma, et al.).
		d. According to a study on rats with experimental arthritis, the leaves of the aforementioned plant may have immunomodulatory effects by reducing oxidative and inflammatory stress. Following treatment with the aforementioned plant's leaves, the animal subjects displayed a significant decrease in inflammation as well as arthritic alterations. (H Lad, et al.).
		d. Blocking COX-2 expressions and the phosphorylation of Akt, IKK, MAPK, and NF-B during the activation of LPS-stimulated macrophages has anti-inflammatory effects. (TY Hu, JM Ju, LH Mo, L Ma, WH Hu, RR You, et al.).

3	Kuberaksha *(Caesalpinia crista* L.)	a. Exhibits antimalarial (SK Kalauni, et al.) and hepato protective (Sarkar, et al.) activity. b. Immuno stimulatory effects include an increase in hemagglutinating antibody titre and a shift in delayed-type hypersensitivity. (S Shukla, A Mehta, et al.). c. Shows anti-vaccinia virus activity (Dhar, et al.). d. Potential for immunomodulation, as evidenced by the positive activation of the neutrophil adhesion test, hemagglutinating antibody (HA) titre, Delayed Type Hypersensitivity (DTH) reaction, phagocytic activity, and cyclophosphamide-induced myelosuppression in an *in* vivo experimental research (S. Shukla, A Mehta, et al.).
4	Katuki (*Picrorhiza kurroa* Royle ex. Benth)	a. Anti-inflammatory effect by l3-adrenergic blockade (BL Pandey, et al.). b. Increases cytokine levels (IL-4 and IFN-gamma) in serum, lymphocyte proliferation, HA titre, DTH, PFC, phagocytic index, and CD4/CD8 population, which strengthens the immune system. (A Gupta, A Khajuria, J Singh, KL Bedi, NK Satti, P Dutt, et al.). c. Stimulates phagocytosis and the immune system's cell-mediated and humoral components in experimental animals (A Hussain et al.). d. Study demonstrates the antioxidant and free radical scavenging activity of the leaf extract (K Kant, M Walia, et al.). e. Inhibits the growth of Plasmodium falciparum significantly (M Lusakibanza, G Mesia, G Tona, S Karemere, A Lukuka, M Tits, et al.).

Table 1. The pharmacological activity of ingredients of AYUSH-64.

Based on the previous effectiveness on infective febrile conditions such as malaria, microfilaraemia, chikungunya, and influenza with no safety issues observed in published clinical studies further AYUSH-64 was repurposed for COVID-19 based on a previous clinical study that showed AYUSH-64 was effective in Influenza like Illness (ILI) and a molecular docking study that revealed 35 phytoconstituents isolated from AYUSH-64 demonstrated anti-viral activity against SARS-CoV-2 [8-13]. During COVID-19, clinical studies have been conducted to explore the therapeutic efficacy of traditional medicines in COVID-19 across the world. In India, traditional medical practices like Ayurveda have been extremely crucial in the prevention and management of COVID-19. Out of 122 trials on COVID-19 recorded in the clinical trial registry of India as of June 2020, the majority (n=67) were registered in the category of traditional medicine as compared to conventional medicine (n=42) [14]. So far total 11 studies were found in which AYUSH-64 was explored to manage COVID-19 conditions as standalone or adjunct to standard care treatment. For these clinical trials, the major outcomes included SARS-CoV-2 clearance determined by a negative RT-PCR assay, efficacy proved in terms of clinical recovery, mean time to clinical recovery, and mean time to clinical recovery. Secondary outcomes include clinical worsening (progression to severe or critical stage), incidence of death, change in pro-inflammatory marker levels, chest imaging findings, and quality of life parameters. Adverse event/adverse drug reaction incidence and changes in hematologic and biochemical markers were the safety outcomes.

Study outcomes

In one study (HR Natraz, et al.) AYUSH-64 was administered to the mild to moderate COVID-19 patients in a dose of 500 mg twice daily after food as adjuvant along with Standard of Care (SOC) as compared to SOC alone, it was found effective and safe in reducing the cardinal symptoms of COVID-19 viz. fever, cough, sore throat, diarrhoea, headache, loss of taste, skin rashes and tiredness [15]. In a single arm pilot study AYUSH-64 was administered in a dose of 500 mg thrice in a day for 7 to 14 days. It was observed that 39.28% of participants experienced a clinical recovery in 7 days; and 53.5% of patients experienced a clinical recovery in 14 days. The mean time for clinical recovery was 7.04 days (± 2.88 day's standard deviation) [16]. Similarly in one more study AYUSH-64 was found effective in terms of clinical recovery, where 86.1% of patients demonstrated clinical recovery following a 14 days intervention with AYUSH-64, of which 75% did so within 7 days. According to the results of the RT-PCR test, 50% of participants went negative on day 8 and 69.4% of individuals became negative up to day 15 [17]. Three Randomized Controlled Trials (RCTs) revealed the percentage of patients who achieved clinical recovery [18-20]. Overall, patients receiving AYUSH-64 in addition to standard therapy (AG) showed improved clinical recovery compared to the control group receiving standard care alone

(CG) (n=386; OR=2.35; 95% CI=1.33 to 4.16; P=0.003) Additionally, COVID-19 patients in AG showed a higher percentage of clinical recovery within 7 days. Although there were a decreased percentage of asymptomatic participants moving into the symptomatic stage in the AG group in one RCT that demonstrated clinical improvement as measured by the WHO ordinal scale, the mean score did not differ significantly across groups. Three studies reported the percentage of subjects who tested COVID-19 negative by RT-PCR. The period of time from day 7 till clinical recovery was used to evaluate the SARS-CoV-2 clearance using an RT-PCR test. Within 14 days, the AG showed improved SARS-CoV-2 clearance.

The changes in the levels of serum pro-inflammatory biomarkers, including C-Reactive Protein (CRP), Ddimer, serum ferritin, interleukin-6, Lactate Dehydrogenase (LDH), and TNF. The levels of pro-inflammatory biomarkers were not significantly different between groups, while significant declines in the levels of the majority of the biomarkers were recorded within groups. According to one study, the effect size of these parameters was larger in the AG compared to CG for D-dimer (0.490 *vs.* 0.431), serum ferritin (0.651 *vs.* 0.565), and CRP level (0.558 *vs.* 0.465). Two studies demonstrated an improvement in the chest imaging findings. According to one study, there was a significant difference between the AG (p-value=0.031) and CG (p-value=0.210) in the HRCT chest CO-RADS score. 12 Additionally, more AG participants had lower CO-RADS category 1 scores on day 30 compared to CG participants (p-value=0.017). Another survey suggests no post-COVID lung problems at the end of the study period, and that the results of the chest skiagram were equivalent in both groups. According to two studies, none of the subjects required oxygen therapy or experienced any side effects including pneumonia, acute respiratory distress syndrome, sepsis, arrhythmia, etc. in AG group. One of the studies that were included revealed changes in quality-of-life metrics. The WHOQOL-BREF scale was used in the study to evaluate overall life quality. Comparing the AG to the CG, there was a clear improvement in the physical health, psychological health, social relationships, and environmental well-being. At the conclusion of the study period, one study showed perceived stress scale values that were comparable in both groups.

Discussion

In another study carried out in India from May 8 to August 31, 2021 to investigate the disease characteristics, care-seeking behaviour during home isolation, clinical outcomes, adverse events, and the relationship between various risk factors and clinical recovery over the course of the study period, a cross-sectional analysis of the data generated by a community study semi-structured questionnaires were used to gather the data, and they were available in an electronic data collection format at the beginning, 7, 14 and 21 days afterwards. To investigate the link between pertinent factors and clinical recovery, a logistic regression analysis was conducted. Baseline analysis was performed on data from 64,642 individuals, while final analysis was performed on data from 49,770 people. The recruited participants' average age was 38.8 11.7 years, and 8.4% of them had co-morbidities. 58.3% of participants added AYUSH-64 to their regular medical treatment. Regarding clinical improvement, disease progression, the need for oxygen supplementation, hospitalisation, admission to the intensive care unit, and the requirement for ventilator support, participants using AYUSH-64 either as a stand-alone treatment or as an addition to standard care experienced comparable clinical outcomes. Early clinical recovery was associated with younger age, no co-morbidities, no substance misuse, and vaccination compared to older age and non-vaccination.

Possible mechanism

The majority of COVID-19 patients exhibit lymphocytopenia, an elevated interleukin concentration, a subnormal or decreased leukocyte count, and tumour necrosis factor-a. Bronchial epithelial cells produce IL-6 in a dose-dependent manner in response to SARS-CoV infection. TLR-7 (Tell like Receptor-7) allows the SARS-CoV-2 virus to infiltrate through ACE2 by activating pro-inflammatory kinases. AYUSH-64 has an acidic pH and is high in phytoacids. Similar to other anti-malarial medications, AYUSH-64's anti-viral actions may be attained by raising the pH of intracellular vacuoles and reducing endosomal activity.

The central metabolism is deregulated in the early immunological response to COVID-19 in order to mobilise energy, cells, and biomolecules. Amadosha (undigested by products of digestion and metabolism) is the Ayurvedic term for this dysregulation of the central metabolism. The Deepana and Pachana qualities of Saptaparna and Katuki (which improve digestion and metabolism) cleanse the Amadosha. In order to produce an antiviral defence response, AYUSH-64 may be reprogramming the host metabolism and controlling enzyme activity and biosynthesis. Additionally, *S. chirata* Pexbex's anti-inflammatory and antioxidant properties enhance its effects. The haemocytic system is activated during the inflammatory phase of COVID-19 by a number of factors, leading to endothelial dysfunction, platelet activation, as well as micro and macrovascular thrombosis. ACE2 and TMPRSS2 receptors are used by human platelets to express. By attaching to these receptors, SARS-CoV-2 and its spike protein directly promote platelet activation. The thrombolytic effect of *P. kurroa* Royle ex. Benth in AYUSH-64 is in accordance with Ayurvedic theory. Another perspective is that D-dimer in critical patients of COVID-19 is elevated and AYUSH-64 decreases the levels of D-dimer significantly.

Conclusion

The components of AYUSH-64 may block the Angiotensin-Converting Enzyme II (ACE2) and Reactive Oxygen Species (ROS), reduce COVID-19's initial symptoms and the cytokine storm, and stop the disease from progressing. In multiple clinical trials, AYUSH-64 has been repurposed for the management of asymptomatic and mild to moderate cases of COVID-19 as a stand-alone therapy or as an addition to normal care, with encouraging outcomes. On the basis of clinical trials conducted it was found that AYUSH-64 used in conjunction with standard care, AYUSH-64 expedites clinical recovery compared to standard care alone, prevents disease progression, and has been demonstrated to be safe in patients with asymptomatic, mild, and moderate COVID-19.

Conflict of Interest

No conflict of interest.

Author's contributions

SB Singh-Concept, data analysis and manuscript writing.

Savita Sahrma-Manuscript review.

Poornima Mansoria-Manuscript writing and editing.

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