Journal of Ayurveda and Integrative Medicine 13 (2022) 100538

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Review Article

AYUSH- 64: A potential therapeutic agent in COVID-19

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ARTICLE INFO

Article history:
Received 9 July 2021
Received in revised form
23 August 2021
Accepted 10 December 2021
Available online 4 January 2022

Keywords:
AYUSH-64
COVID-19
Corona virus disease
Immunomodulation
SARS-CoV-2
Ayurveda

ABSTRACT

Corona Virus disease (COVID-19) has become a global pandemic resulting in large scale morbidity and mortality worldwide. The management of COVID-19 has been a big challenge because of multifactorial pathophysiology and no specific treatment. AYUSH-64, a poly-herbal formulation developed by CCRAS, Ministry of AYUSH, Govt. of India through extensive pharmacological, toxicological and clinical studies has proven its safety and efficacy in infective febrile conditions such as malaria and influenza. AYUSH- 64 has four ingredients having immunomodulatory, anti-inflammatory, antipyretic, antioxidant and anti-viral activities. It arrests the extreme inflammatory responses in COVID-19 that causes progression to significant morbidity. AYUSH-64 has also been incorporated in the National COVID management protocol based on Ayurveda and Yoga by Government of India for asymptomatic and mild cases of COVID-19. Further, on the basis of tangible evidence generated through robust clinical and experimental studies on AYUSH-64, the Ministry of AYUSH has launched nation-wide campaign for mass distribution of AYUSH-64 to asymptomatic, mild to moderate COVID-19 patients in home isolation to reduce the burden on the hospital. This review will highlight the specifications of AYUSH-64, its mechanism of action, its repurposing for COVID-19, various clinical and experimental studies.

1. Introduction

Historically, outbreak of infectious diseases offers some model of the course of diseases and treatment such as Spanish flu, Bird flu etc. that unfold over the time. Some diseases have predictable seasonal peaks with high transmission as some pathogen may spread rapidly in dynamics of humidity, social mixing pattern leaving predictable pattern for each variant. The 'wave' of COVID-19 and its implications is the prominent topic of debate in current times. An epidemic wave/phase is defined as natural pattern of peaks and valleys which indicate the number of sick people and deaths in given time and then decline [1]. The first wave peaked in India in September 2020 and second wave started from 1st week of March 2021. The tragedy of second wave of COVID-19 and its impact on health care systems of our nation has been devastating and unprecedented [2]. There could be several factors responsible for the increased number of cases in the second wave. It is observed that the mutant strain of SARS-CoV-2 has higher transmission capability in addition to lesser incubation period. There has been a widespread disregard to the 'COVID Appropriate Behavior' by the general public, resulting in manifestation of severe illness, reduction in neutralizing antibodies and reduced effectiveness of vaccination.

The Ministry of AYUSH (MoA), Government of India has taken several public health and R&D initiatives to explore the potential of AYUSH systems to mitigate the impact of COVID-19 pandemic. Different institutions under the Ministry of AYUSH in collaboration with prominent medical and research organizations across the country to undertake research on COVID-19 through various AYUSH systems. The MoA constituted an inter-disciplinary AYUSH R&D Task Force consisting of scientists, pulmonologists, epidemiologists, pharmacologists etc., from premier organizations and research institutions to handle various aspects of clinical and experimental research through AYUSH interventions. The Ministry of AYUSH also recommended a set of self-care guidelines for preventive health measures, with special emphasis on respiratory health and improving general immunity. The Ministry of AYUSH further issued the National Clinical Management Protocol based on

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Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2021.100538

Ayurveda & Yoga for management of COVID -19 to enable uniform clinical management [3]. The management guidelines advised in the protocol are based on the interim trends and outcomes of AYUSH COVID-19 studies along with the published evidence related to the safety and potential benefits of Ayush interventions.

2. Brief about AYUSH-64

AYUSH-64, a polyherbal formulation developed by Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH through extensive pharmacological, toxicological and clinical studies. It has proven saftey and efficacy in infective febrile conditions such as malaria, microfilaremia, chikungunya and influenza [4–9]. Further, AYUSH 64 was found safe and non-toxic in a dose of 500 mg/kg body weight for 12 weeks in experimental studies [10,11]. Quality control and safety parameters of the ingredients of AYUSH-64 and the final formulation is in complience with the Ayurveda Pharmacopoeia limits. The constituents of AYUSH-64 viz. *Saptaparna* (*Alstonia scholaris* R. Br.), *Katuki* (*Picrorhiza kurroa* Royle ex. Benth), *Kiratatikta* (*Swertia chirata* Pexbex. Karst) and *Kuberaksha* (*Caesalpinia crista* L.) are reported to possess immunomodulatory, anti-inflammatory, antipyretic, antioxidant and anti-viral activities [12–17]. These effects could inhibit the extreme inflammatory responses in COVID-19 that causes progression to significant morbidity. In a prospective, open-label, non-randomized pre-test and post-test design pilot study on AYUSH-64 in Influenza like Illness (ILI), one-week intervention of AYUSH-64 in a dose of 3 gm/day provided early clinical recovery from 'Influenza Like Illness' (ILI) symptoms with reduced frequency of usage of acetaminophen/antihistaminic [9]. The results of a Molecular Docking study revealed that the presence of M^{pro}–Akuammicine N-Oxide with highest M^{pro} binding energy along with other 34 phyto-constituents having similar anti-viral activity against SARS- CoV-2 as part of AYUSH-64 make it a suitable drug/medicine for repurposing for the COVID-19 management [18].

2.1. New indication for COVID-19

AYUSH-64 was repurposed for COVID-19 based on the recommendations of Interdisciplinary AYUSH R & D Task Force constituted by the Ministry of AYUSH along with available quality standards, evidences on clinical and pre-clinical safety [4–8,10,11], evidences on efficacy in Influenza-like illness [9]. The new indication was based on anti-viral and immune–modulator activity [12–16] as well as evidences drawn through molecular docking study discussed in previous section [17]. As per the clinical trial registry of India, total seven clinical studies on AYUSH-64 in asymptomatic and mild to moderate COVID-19 cases were undertaken by reputed medical institutions across the country. AYUSH-64 was administered in the management of asymptomatic & mild cases of COVID-19 as standalone treatment and for the management of mild and moderate COVID-19 as an adjunct to standard care in these clinical trials. The outcomes of these studies demonstrated that AYUSH-64 as adjunct treatment to standard care resulted in early clinical recovery compared to standard of care alone without progression of the disease to severe or critical stage [18–21]. The mean time to negative RT-PCR assay for COVID-19 was also better in the AYUSH-64 add-on group [18,20]. Also, there was improvement in Quality of life (QoL) parameters [18]. AYUSH-64 was found to be well tolerated and safe.

Based on the leads generated through experimental and clinical studies, AYUSH-64 has been incorporated in the National COVID management protocol based on Ayurveda and Yoga for asymptomatic and mild cases of COVID-19 [3]. AYUSH-64 is further included in the “Guidelines for Ayurveda Practitioners for COVID-19 Patients in Home Isolation” issued by the Ministry of AYUSH during the second outbreak of COVID-19 in the country [22]. The Ministry of AYUSH has also launched nation-wide campaign for mass distribution of *AYUSH-64* to asymptomatic, mild to moderate COVID-19 patients in home isolation to reduce the burden on the hospital-based health care delivery system [23].

The objective of this review is to scientifically explain the general therapeutic approach of AYUSH-64 to intervene in disease progression during various clinical and pathogenic stages of COVID-19.

3. COVID-19: window of transmission and infection dynamics

SARS-CoV-2 virus spreads through respiratory droplets of infected individuals. The average incubation period ranges from 1 to 14 days and mean is 5–6 days [24]. The infectivity is higher during initial period of infection; however patient can remain for an average of two weeks. The window of infected state varies from person to person; some individual may remain infected for several weeks and remain asymptomatic are known as long term spreader. A large proportion of individuals affected with COVID-19 are infected either with pre-symptomatic or with asymptomatic transmission. So, keeping track of these variants is very vital for this pandemic control. Nearly 80% persons have been asymptomatic or display mild symptoms, 15% display moderate to severe symptoms and require oxygen support and 5% patients have been critical with an immediate need for mechanical ventilation even during second outbreak of COVID-19. The mortality varies from country to country and is approximately 11% worldwide in hospitalized patients, although it was less than 1.1% in India [25].

The viral dynamics reveal that there is no difference between viral load and severity of COVID-19 and its clinical outcome. The infection clears by itself in early stage in mild cases, while severe cases have prolonged viral shedding. The studies so far have shown conflicting evidence in regard to the viral shedding kinetics. The patient can continue to shed the virus even after the symptom resolution. The mean duration of viral shedding is 20 days among the survivors. It has also observed that some patients with mild symptoms of COVID-19 initially can suffer from variable and debilitating symptoms for more than two months of the initial infection referred as long-term effects of COVID-19 [26].

3.1. COVID-19: clinical features and immune response

The clinical features vary from patients to patient depending on the individual's immune response. The clinical category of COVID-19 include asymptomatic (positive RT-PCR without symptoms), mild to moderate (positive with clinical manifestations) or severe and critical (positive with high degree of manifestations). The common symptoms of COVID-19 include fever (83–98%), fatigue (70%), dry cough (82%), headache (34%), dyspnea (50%), sore throat (14%), rhinorrhea (7%), anosmia (Loss of smell) and ageusia (Loss of taste) (<7%), diarrhea (20%), vomiting (14%) and weakness (70%) in the hospitalized patients [27–29] along with a significant increase of C- reactive protein (>20 mg/dl). The CRP concentration is worse in severe (>40 mg/dl) and critical cases (>100 mg/dl) compared to mild cases (<18 mg/dl) [30]. The raised absolute lymphocyte count (<100 cells/μl) is also found in severe patients [31].The increased respiratory rate >30/min and SpO 2 <90% are the indicators of severe COVID-19. Some patients proceed to critical stage as observed by systemic inflammation due to cytokine storm and widespread platelet aggregation leading to multi-organ failure as the end stage of COVID-19.

An infected person initially moves through stage of replication over first few days followed by a stage of adaptive immunity over

the next few days. In the replication stage, the virus replication leads to flu-like illness characterized by mild symptoms due to direct cytopathic effect (structural changes in host cells) of the virus. In the stage of adaptive immunity, virus levels decline as immune system takes over, but in inflammatory phase, there is a possibility of cytokine storm leading to tissue destruction and clinical deterioration [32].

3.2. Pathological progression of COVID-19

To develop effective therapeutics and preventive measures against COVID-19, an accurate and precise understanding of its pathogenesis at the molecular level is needed. Based on the most recently published literature, the overall COVID-19 pathogenesis process can be summarized as three clinically distinct and potentially overlapping phases. As shown in Fig. 1, its pathological progression can be classified in chronological order as viral replication or early infection, pulmonary, pro-inflammatory, and pro-thrombotic phases [33].

4. Mechanism of action of AYUSH-64

The chemical constituents and therapeutic indications of the four ingredients of AYUSH-64 are given in Table 1. As per the published evidence, the ingredients of AYUSH-64 have the potential to control the initial symptoms of COVID-19, mitigate the cytokine storm through the inhibition of cytokines, inhibition of Angiotensin-Converting Enzyme II (ACE2) and Reactive Oxygen Species (ROS).

4.1. Anti viral activities isolated molecules of AYUSH-64

The isolated molecules of medicinal plants present in AYUSH-64 have antiviral activities against COVID-19 through potentiate the production of arginine (Amino acid) to inhibit the activity of spike glycoprotein of SARS-CoV-2 as well as ACE2. The α-amyrin and Alstonides present in saptoparna, amarogentin, eufoliatorin, kutkin present in Katiki and caesalpinins in Kuberakshya (Table- 1) are the top ranked molecules with highest affinity towards both the spike glycoprotein and ACE2 [34]. In addition AYUSH-64 as add on treatment with conventional care is reported to be effective in reducing the duration of symptometic stage [35].

4.2. Effect of AYUSH-64 in SARS-CoV-2 induced pro-inflammatory process

The majority of COVID-19 patients have subnormal or reduced leucocyte count, lymphocytopenia, increased concentration of interleukins and tumour necrosis factor α. Interleukin (IL-6) is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells. SARS-CoV-2 virus enters through ACE2 via TLR-7 (Tell like Receptor-7) which activates the pro-inflammatory kinases. AYUSH -64 is rich in phytoacids and has acidic pH. The anti-viral activities of AYUSH-64 may be achieved by increasing pH of intra-cellular vacuoles and decreased endosomal activities similar to other anti-malarial drugs [34]. The immediate immune responses to COVID-19 are deregulation of central metabolism for mobilization of energy, cells and biomolecules [35–38]. This deregulation of central metabolism is called *Amadosha* (undigested byproducts of digestion and metabolism) in Ayurveda. *Saptaparna* and *Katuki* have *Deepana* and *Pachana* properties (enhancing digestion and metabolism) which clear the *Amadosha*. So, AYUSH-64 may be reprogramming the host metabolism and regulate the enzymatic activities and biosynthesis to generate antiviral defense response. Moreover, anti-inflammatory and antioxidant activities of *S. chirata Pexbex. Karst* potentiates its action [39].

4.3. Effect of AYUSH-64 on potential agents for pulmonary impairment

COVID-19 begins in upper respiratory tract but replicates quickly in ACE2 receptor rich respiratory mucosa. After reaching the alveoli, virus begins to replicate fast in pneumocytes causing cell death. This cellular damage accelerates the appearance of multinucleated giant cells and fibrin rich hyaline membrane. All the phytoconstituents of AYUSH-64 have cough and dyspnea relieving properties which reverse the inflammatory process and reduce

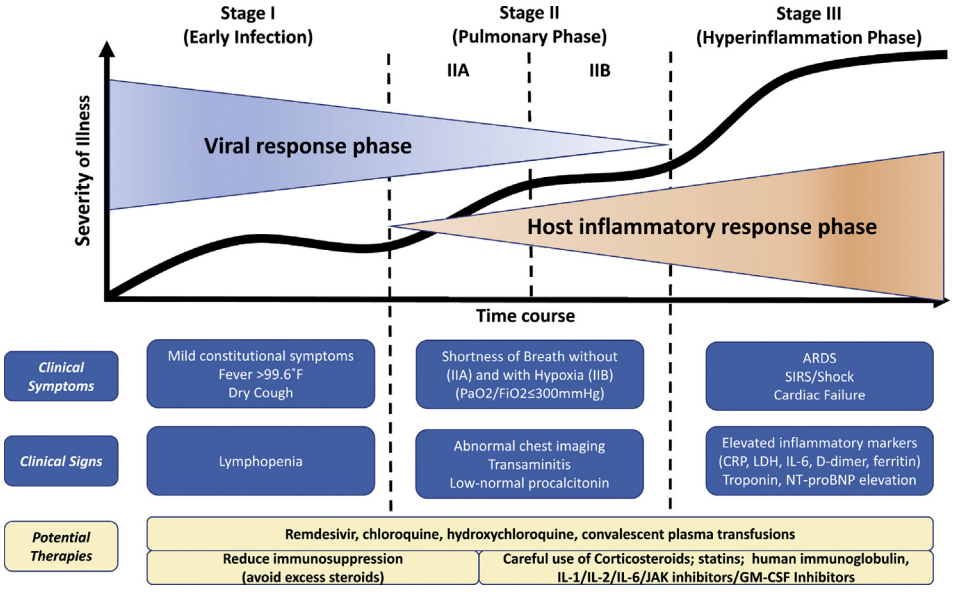

Fig. 1. Clinical stages of COVID-19.

Table 1
Chemical constituents and indications of four constituents in AYUSH-[64].

Name of the Medicinal Plant	Major chemical constituents	Indication as per Ayurveda
Saptaparna (*Alstonia scholaris* R. Br.)	Akuammicine N-Oxide, Akuammiginone, Echitaminic acid Echitamidine N-oxide, Alstonides, alpha -amyrin	Jvara (disease conditions associated with pyrexia), *Kasa*(cough), *Swasa* (dyspnea), *Pravahika* (dysentry)
Katuki (*Picrorhiza kurroa Royle ex. Benth)*	Picroside I and II, kutkoside, cucurbitacins, vanillic acid, cinnamic acid, ferulic acid apocynin, saptoparna, amarogentin, eufoliatorin, kutkin	*Visamajvara* (disease conditions associated with recurrent pyrexia), *Kasa* (cough), *Swasa*(dyspnea)
Kiratatikta (*Swertia chirata Pexbex. Karst)*	Xanthine, Xanthine glycoside, flavonoids, iridoid glycocide, triterpenoid	*Visamajvara* (disease conditions associated with recurrent pyrexia), *Kasa* (cough), *Swasa*(dyspnea)
Kuberaksha (Caesalpinia crista L.)	Diterpines, caesalpinin N, Diterpenoids, Casalmin, NonCasalpine-E, caesalpinins	*Jvara* (disease conditions associated with pyrexia), *Kasa*(cough), *Swasa*(dyspnea), *Sopha*(inflammation)

fibrosis. The concept of *Pramathi* (clearing property of cell debrides) is extremely useful for downward regulation of fibrin deposition. The alkaloids from *A. scholaris* R. Br. inhibit Influenza A virus replication and lung immunopathology by regulating the innate immune response [40,41]. Research studies found that Neutrophil Extracellular Traps (NET) is the main culprit of pulmonary dysfunction and AYUSH-64 decreases the total neutrophil counts of COVID-19 patients. The clinical indicators of COVID-19 patients (fever, cough and dyspnea) decreased in AYUSH-64 group indicating that AYUSH-64 has a promising efficacy in preventing lung impairment [42–45]. *C. crista* L. has excellent therapeutic potential to reduce fever, cough and clears the lungs [46].

4.4. Effect of AYUSH-64 in SARS-CoV-2 induced hyperinflammatory and prothrombin phase

The inflammatory phase of COVID-19 passes through various mediators activating haemocytic system through endothelial dysfunction, platelet activation in addition to micro and macro vascular thrombosis. Human platelets express through ACE2 and TMPRSS2 receptors. SARS-CoV-2 and its Spike protein directly enhance the platelet activation by binding to these receptors [47]. *P. kurroa* Royle ex. Benth in AYUSH-64 possess thrombolytic action as described in Ayurveda. Another view is that there is an elevation of D-dimer in critical patients of COVID-19 and AYUSH-64 decrease the levels of D-dimer significantly. Immunosuppressive effect *of S. chirata Pexbex. Karst* may reduce the inflammatory process [48].

5. Conclusion

The ingredients of AYUSH-64 have the potential to control the initial symptoms of COVID-19 and the cytokine storm, inhibition of the Angiotensin-Converting Enzyme II (ACE2) and Reactive Oxygen Species (ROS) and thereby prevention of the progression of COVID-19. Taking leads from the outcomes of clinical study on influenza-like illness and molecular docking study, AYUSH-64 has been repurposed for the management of asymptomatic and mild to moderate cases of COVID-19 as standalone therapy or adjunct to standard care in several clinical trials with promising results. Thus, AYUSH- 64 could play a significant role in reducing the large-scale morbidity associated with COVID-19 and reduce the burden on the hospital-based health care delivery system by effectively managing the home-isolated cases.

Source of funding

Nil.

Conflict of interest

None.

Author contributions

Contribution of Dr. A.K. Panda - Create a concept to write a review article and prepare the model. Creation of research group and preparation of initial draft. Worked as corresponding author after all the authors agreed for it. Contribution of Dr. S. Kar - Help in preparation of initial draft. Oversight of the manuscript. Contributions of A.K. Rai - Collection of evidence and computing the data and writing of final manuscript. Contribution by BCS Rao - supervision the manuscript and help in writing the final draft. Contributions of N. Srikanta - Mentorship and leadership of the core idea, supervision of the manuscript, set the title and approve the final draft.

References

[1] Dhar Chowdhury S, Oommen AM. Epidemiology of COVID-19. J Dig Endosc 2020;11(1):3–7. https://doi.org/10.1055/s-0040-1712187.
[2] Jain VK, Iyengar KP, Vaishya R. Differences between First wave and Second wave of COVID-19 in India [published online ahead of print, 2021 May 8]. Diabetes Metab 2021;S1871–4021(21):147–8. https://doi.org/10.1016/j.dsx.2021.05.009.
[3] Ministry of Ayush, Government of India. National clinical management protocol based on Ayurveda and Yoga for management of Covid-19. 2020. Available from: https://www.ayush.gov.in/docs/ayush-Protocol-covid-19.pdf.
[4] Chari MV, Venkataraghavan S, Seshadri C, Shetty BR, Gowri N. A double-blind clinical trial with Ayush-64 an Ayurvedic drug in *P. vivax* Malaria. J Res Ay Sid 1982;6(3–4):105–16.
[5] Bhatia D. Role of AYUSH-64 in malaria epidemic. J Res Ay Sid 1997;18(1- 2): 71–6.
[6] Sharma KD, Kapoor ML, Vaidya SP, Sharma LK. A clinical trial of "Ayush-64" (A coded antimalarial medicine) in cases of malaria. J Res Ay Sid 2017;II(4).
[7] Pandey PN, Kishore P. Effect of Ayush-64 and SaptaparnaghanaVati on microfilaraemia. J Res Ay Sid 1989;12(3–4):145–50.
[8] Anonymous. Management of chikungunya through Ayurveda and Siddha- A technical report. Central Council for Research in Ayurvedic Sciences, Department of Ayush, Ministry of Health & Family Welfare, Government of India; 2009.
[9] Gundeti MS, Bhurke LW, Mundada PS, Murudkar S, Surve A, Sharma R, et al. AYUSH 64, a polyherbal Ayurvedic formulation in influenza like illness: results of a pilot study. J Ayurveda Integr Med 2020. https://doi.org/10.1016/j.jaim.2020.05.010.
[10] Anonymous. Ayush-64 A new ayurvedic anti- malarial compound. Central Council for Research in Ayurveda and Siddha, Ministry of Health & Family Welfare, Govt. of India; 1987.
[11] Anonymous. Pharmacological investigations of certain medicinal plants and compound formulations used in Ayurveda and siddha. Central Council for Research in Ayurveda and Siddha, Ministry of Health & Family Welfare, Govt. of India; 1996.
[12] Zhao YL, Shang JH, Pu SB, Wang HS, Wang B, Liu L, et al. Effect of total alkaloids from Alstonia scholaris on airway inflammation in rats. J Ethnopharmacol 2016;178:258–65. https://doi.org/10.1016/j.jep.2015.12.022.
[13] Hu TY, Ju JM, Mo LH, Ma L, Hu WH, You RR, et al. Anti-inflammation action of xanthones from Swertia chirayita by regulating COX-2/NF-κB/MAPKs/Akt signaling pathways in RAW 264.7 macrophage cells. Phytomedicine 2019;55: 214–21. https://doi.org/10.1016/j.phymed.2018.08.001.
[14] Shukla S, Mehta A, Mehta P, Vyas SP, Shukla S, Bajpai VK. Studies on anti-inflammatory, antipyretic and analgesic properties of *Caesalpinia bonducella* F. seed oil in experimental animal models. Food Chem Toxicol 2010;48(1):61–4. https://doi.org/10.1016/j.fct.2009.09.015.
[15] Gupta A, Khajuria A, Singh J, Bedi KL, Satti NK, Dutt P, et al. Immunomodulatory activity of biopolymeric fraction RLJ-NE-205 from Picrorhiza kurroa. Int

Immunopharm 2006;6(10):1543–9. https://doi.org/10.1016/j.intimp.2006.05.002.
[16] Kumar R, Gupta YK, Singh S, Raj A. Anti-inflammatory effect of Picrorhiza kurroa in experimental models of inflammation. Planta Med 2016;82(16):1403–9. https://doi.org/10.1055/s-0042-106304.
[17] Ram TS, Munikumar M, Raju VN, Devaraj P, Boiroju NK, Hemalatha R, et al. In silico evaluation of the compounds of the ayurvedic drug, AYUSH-64, for the action against the SARS-CoV-2 main protease. J Ayurveda Integr Med 2021. https://doi.org/10.1016/j.jaim.2021.02.004.
[18] Chopra A, Chavan-Gautam P, Tillu G, Saluja M, Borse S, Sarmukaddam S, et al. Coadministration of AYUSH 64 as an adjunct to Standard of Care in mild and moderate COVID-19: a randomised, controlled, multicentric clinical trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.06.12.21258345v1.
[19] Reddy RG, Gosavi RV, Yadav B, Rai AK, Holay MP, Talekar M, et al. AYUSH- 64 as an add-on to standard care in asymptomatic and mild cases of COVID- 19: a randomized controlled trial. Preprint available at: https://osf.io/pgraf/.
[20] Singh H, Srivastava S, Yadav B, Rai AK, Jameela S, Muralidharan S, et al. AYUSH- 64 as an adjunct to Standard Care in mild to moderate COVID-19: an open-label randomized controlled trial in Chandigarh, India. Preprint available at: https://osf.io/xyuas/.
[21] Bhardwaj P, Godatwar PK, Charan J, Sharma S, Shafi S, Chauhan N, et al. Efficacy and safety of ayurveda intervention (AYUSH 64) as add-on therapy for patients with COVID-19 infections – an open labelled, parallel group, randomized controlled clinical trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.08.10.21261836v1; 2021.
[22] Ministry of Ayush. Government of India. Ayurveda preventive measures for self- care during COVID-19 pandemic. Available from: https://covid19.india.gov.in/document/ayurveda-preventive-measures-for-self-care-during-covid-19-pandemic/; 2021.
[23] Press Information Bureau. Government of India. Ayush Ministry launches nationwide distribution campaign of AYUSH 64 & Kabasura Kudineer. Available from: https://pib.gov.in/Pressreleaseshare.aspx?PRID=1716729; 7th May 2021.
[24] Machhi J, Herskovitz J, Senan AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol 2020;15(3):359–86. https://doi.org/10.1007/s11481-020-09944-5.
[25] Carbone M, Lednicky J, Xiao SY, Venditti M, Bucci E. Coronavirus 2019 infectious disease epidemic: where we are, what can Be done and hope for. J Thorac Oncol 2021;16(4):546–71. https://doi.org/10.1016/j.jtho.2020.12.014.
[26] Zacharioudakis IM, Prasad PJ, Zervou FN, et al. Association of SARS-CoV-2 genomic load with outcomes in patients with COVID-19. Ann Am Thorac Soc 2021;18(5):900–3. https://doi.org/10.1513/AnnalsATS.202008-931RL.
[27] Jiang F, et al. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med 2020;35:1545–9. https://doi.org/10.1007/s11606-020-05762.
[28] Sharma R, Agarwal M, Gupta M, Somendra S, Saxena SK. Clinical characteristics and differential clinical diagnosis of novel coronavirus disease 2019 (COVID- 19). Coronavirus Disease 2019 (COVID-19) 2020:55–70. https://doi.org/10.1007/978-981-15-4814-7_6. Published 2020 Apr 30.
[29] Romagnoli S, Peris A, De Gaudio AR, Geppetti P. SARS-CoV-2 and COVID- 19: from the bench to the bedside. Physiol Rev 2020;100(4):1455–66. https://doi.org/10.1152/physrev.00020.202.
[30] Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol 2020;92(11):2409–11. https://doi.org/10.1002/jmv.26097.
[31] Wagner J, DuPont A, Larson S, Cash B, Farooq A. Absolute lymphocyte count is a prognostic marker in Covid-19: a retrospective cohort review. Int J Lab Hematol 2020;42(6):761–5. https://doi.org/10.1111/ijlh.13288.
[32] Oliveira DS, Medeiros NI, Gomes JAS. Immune response in COVID-19: what do we currently know? Microb Pathog 2020;148:104484. https://doi.org/10.1016/j.micpath.2020.104484.
[33] Yu C, Zhou M, Liu Y, et al. Characteristics of asymptomatic COVID-19 infection and progression: a multicenter, retrospective study. Virulence 2020;11(1):1006–14. https://doi.org/10.1080/21505594.2020.1802194.
[34] Maurya VK, Kumar S, Bhatt MLB, Saxena SK. Antiviral activity of traditional medicinal plants from Ayurveda against SARS-CoV-2 infection [published online ahead of print, 2020 Oct 19]. J Biomol Struct Dyn 2020:1–17. https://doi.org/10.1080/07391102.2020.1832577.
[35] Thakar A, Panara K, Patel F, Bhagiya S, Goyal M, Bhinde S, et al. Add-on Ayurveda treatment for early stage COVID-19: a single center retrospective cohort study from Gujarat, India. J Evid Based Integr Med 2021;26. https://doi.org/10.1177/2515690X211020685. 2515690X211020685.
[36] Cheng S-C, Joosten LAB, Netea MG. The interplay between central metabolism and innate immune responses. Cytokine Growth Factor Rev 2014;25:707–13. https://doi.org/10.1016/j.cytogfr.2014.06.008.
[37] Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012;487:477–81.
[38] Singh N, Suthar B, Mehta A, Nema N, Pandey A. Corona virus: an immunological perspective review. Int J Immunol Immunother 2020;7:050. https://doi.org/10.23937/2378-3672/1410050.
[39] Das SC, Bhadra S, Roy S, Saha SK, Islam MS, Bachar SC. Analgesic and anti-inflammatory activities of ethanoic root extract of *Swertia chirata* (Gentianaceae). Jordan J Biol Sci 2012;5:31–6.
[40] Zhou HX, Li RF, Wang YF, Shen LH, Cai LH, Weng YC, et al. Total alkaloids from *Alstonia scholaris* inhibit influenza a virus replication and lung immunopathology by regulating the innate immune response. Phytomedicine 2020;77:153272. https://doi.org/10.1016/j.phymed.2020.153272.
[41] Nguyen PQ, Ooi JS, Nguyen NT, et al. Antiviral cystine knot α-amylase inhibitors from alstoniascholaris. J Biol Chem 2015;290(52):31138–50. https://doi.org/10.1074/jbc.M115.654855.
[42] Najmi A, Javed D, Ray A, Sadasivam A. Review of antiviral activities present in some Indian medicinal plants – can they be used against SARS-CoV-2? Int Arch BioMed Clin Res 2020;6(4):RA1–5.
[43] Turaskar A, More S, Sheikh R, Gadhpayle J, Bhongade SL. Inhibitory potential of *Picrorhizakurroa* royle ex. benth extracts on phenylhydrazine induced reticulocytosis in rats. Asian J Pharmaceut Clin Res 2013;6(2):215–21.
[44] Zhang DK, Yu JJ, Li YM, et al. A *Picrorhiza kurroa* derivative, picroliv, attenuates the development of dextran-sulfate-sodium-induced colitis in mice. Mediat Inflamm 2012;2012:751629. https://doi.org/10.1155/2012/751629.
[45] Kumar V, Singh SB, Singh S. Pharmacological Perspectives of Ayurvedic herbs viz. *Alstonia scholaris L.*, *Picrorhiza kurroa*, *Swertia chirata* and *Caesalpinia crista* against COVID- 19: a Mini-Review. Mini-Reviews Org Chem 2021;18:1–9. https://doi.org/10.2174/1570193X17999201102200944.
[46] Eric Wei Chiang entitled *Caesalpinia Crista*. A costal woody Climber with promising therapeutic values. J Appl Pharmaceut Sci 2018;8(3):133–40. https://doi.org/10.7324/JAPS.2018.8319.
[47] Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol 2020 Sep 4;13(1):120. https://doi.org/10.1186/s13045-020-00954-7.
[48] Ahirwal L, Singh S, Bharti V, Mehta A. Immunosuppressive effect of *Swertia chirata* Buch Ham. on Swiss albino mice. Int J Pharma Sci Res 2013;4(12):4763–8. https://doi.org/10.13040/IJPSR.0975-8232.4(12).4763-68.