

A RANDOMIZED CONTROLLED CLINICAL TRIAL TO EVALUATE THE POTENTIAL OF AYURVEDIC MEDICINES IN PATIENTS WITH MILD SYMPTOMS OF COVID-19.

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ABSTRACT:

Objective: The pandemic of COVID-19 has affected globally and impacted hugely in terms of mortality and morbidity. India is seeing a continuous rise in the number of cases. Ayurveda has suggested many remedies which hold potential to manage COVID 19. The present study is clinical trial to evaluate potential of Ayurvedic formulations such as Chyawanprash Sugar free (SF) and ICB03 in COVID 19 patients along with standard of care as per ICMR.

Materials and methods: 90 subjects were enrolled and were grouped into 3 arms as control, Chyawanprash SF and ICB03. Evaluation of serum level of immunological panel CD4, CD8, NK cell panel CD16/CD56 cell counts, inflammatory mediator like CRP, IL-6, and TNF alpha were carried out along with the assessment of clinical symptoms. The trial duration was of 28 days, the primary assessment was done on screening and on day 21. A telephonic follow up was carried out on day 28 to understand the symptoms and clinical status of the subjects.

Results: Treatment with ICB03 and Chyawanprash SF demonstrated that around 50% of subject's subjects were relieved of cough, shortness of breath and fatigue more effectively and in around 7 days which is short period of time than only standard of care. Subjects with ICB03 and Chyawanprash SF treatment presented improved overall quality of life and early recoveries. There was significant improvement in immunological status of

subjects with the treatment of Chyawanprash SF and ICB03. Both Ayurvedic intervention treatment reduced CRP, IL-6, TNF alpha levels.

Conclusion: The outcome of this study was reduction in the time to recovery in clinical symptoms, increased CD3, CD4 and natural killer cells and decreased in elevated serum levels of CRP, Il-6 and tumour necrosis factor alpha (TNF- α). This study confirms safety of Chyawanprash SF and ICB03 in treatment of COVID 19 with no evident adverse effects as well as excellent tolerability.

Key words: COVID-19, Ayurveda, Chyawanprash; Immunity

INTRODUCTION:

The pandemic of COVID-19 has affected globally and impacted hugely in terms of mortality and morbidity. India is seeing a continuous rise in the number of cases as of 29 March 2021 there are around 12 million confirmed cases in India with 162000 deaths. Cases of COVID-19 worldwide have gone up to 127 million with 2.78 million unfortunate fatalities (1). Direct person-to-person transmission occurs through close contact, through respiratory droplets. These droplets may also be the cause of infections through surface contact. The onset of symptoms starts after around 2 days of infectivity and lasts up to 8-10 days. Clinical features include fever, cough, other upper respiratory symptoms, myalgia, diarrhea, loss of taste and smell, fatigue and dyspnea (2). COVID-19 demonstrates increased levels of pro-inflammatory cytokines which are associated with pulmonary inflammation and can lead to pathophysiology of severe lung damage. Thus, cytokine storm is positively correlated with disease severity (4).

The primary therapy currently being used in COVID-19 treatment is a mixture of antiviral drugs, anti-malarial and antibiotics. As measures to fight the novel COVID-19 are researched, emphasis is being placed on reducing the cytokine storm and immunity building benefits of COVID-19 treatment. The integrated Ayurveda can present double benefit of building immunity to fight infection phase by modulating host response and reducing the complications and prognosis of disease into severe stages. Epidemics have not been new to India. Ayurveda has recorded its valuable experiences of epidemics & termed them as Janapadodhwamsa [1, Vimana Sthana 3/1–4] or Maraka [2, Sutra Sthana 6/19]. It has vividly described their mechanism of causation (Nidana), factors affecting severity and actions complicating illnesses, their management and prevention. There are many therapeutic targets researched from SARS and MERS can provide link that many of the Ayurveda based formulations can prove beneficial as protease inhibitors, work as immunomodulator, can improve host dynamics towards spike proteins etc. The aim of the present research was to evaluate safety and efficacy of two Ayurveda based formulations in mild to moderate patients of COVID-19. Shree Baidyanath Ayurved Bhawan Pvt. Ltd. has developed Ayurvedic formulations such as Chyawanprash Sugar free (SF) and ICB03 liquid with the ingredients which can be having potential to modulate immunity of subjects on innate and acquired level and thus can be useful in the management of COVID 19 by modulating host immunity for faster clinical recovery and better prognosis of the disease. Hence the present study was planned as using these formulations in mild COVID 19 patients as an add-on therapy to their conventional treatment laid down by ICMR protocol.

MATERIALS AND METHODS:

Materials:

The interventions used in the clinical trial were Chyawanprash Sugar Free which is formulated by processing around 50 medicinal herbs and their extracts, including the prime ingredient, *Amla* (Indian gooseberry). The finished product has a fruit jam-like consistency, and a sweet, sour, and spicy flavor. It was to be taken in dose of 12-24g orally along with water or milk. Second product under investigation was Polyherbal Immune Booster formulation (ICB03) consisting of *Andrographis paniculata*, *Curcuma longa*, *Glycyrrhizaglabra*, *Ocimum sanctum* as key ingredients out of total 11 ingredients. The dose was 40 ml thrice a day with warm water.

Inclusion Criteria

Patients of either sex, age between 18 to 75 years, COVID positive by RTPCR test and with mild or very mild and presenting fever and/or upper respiratory tract illness were included in the study. The patients with no difficulty in swallowing oral medications and who agreed not to enroll in another study of an investigational agent prior to completion of the study were recruited.

Exclusion Criteria:

Patients who were known to be allergic to drug excipients and with weight less than 40 kg were excluded from the studies. Patients with/without signs of severe disease and with ADRs of septic shock were not considered for enrollment in the study. The patients who have participated in other clinical trials within 1 month and known with impaired renal function were excluded from the study.

Study procedure:

The proposal was approved by Institutional ethics committee of Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India. After approval from IEC, the clinical study was registered on CTRI website with registration number CTRI/2020/10/028537. A total 90 subjects were recruited and were grouped as 30 subjects in each group. Group 1 was control group and received standard care of treatment alone. Group 2 received sugar free Chyawanprash while group 3 received (ICB03) along with standard of care medication suggested by ICMR. The primary objective of the study was to evaluate serum level of immunological CD4, CD8, NK cells, CD16/CD56 cell counts. The levels of inflammatory mediator like CRP, IL-6, and TNF alpha were also assessed. The assessment of clinical symptom such as fever, cough, breathlessness, fatigue and myalgia, loss of taste and smell was also done. The secondary objective of the study was to evaluate the changes in random blood sugar, hematological parameters like WBS, RBC and platelet count for safety assessment of the formulations. The patients were monitored for the improvement/deterioration in health status, day of hospitalization and development of severe symptoms requiring hospitalization in ICU. The trial duration was of 28 days, the primary assessment was done on the day of enrollment the biochemical and immunological tests were performed on 21st day of registration. A telephonic follow up was carried out up to 28th day to understand the symptoms and clinical status of the subjects.

STATISTICAL ANALYSIS:**Sample size consideration:**

Sample size calculation was derived taking considerations of primary and secondary outcomes by a qualified statistician with references of other clinical trials in the same domain with SPSS 10.0.

RESULTS AND OBSERVATIONS:

In the present study, age of patients was ranging from 21.00 –55.00 years. Average age of males in control, Chyawanprash SF and ICB03 groups were 31.71, 33.47 and 33.61 years. Average age of females in control, Chyawanprash SF and ICB03 groups were 31.85, 33.1 and 42.4 years. The percentage of patients with concomitant illness in control, Chyawanprash SF and ICB03 were 26.7 %, 33 %, 30 % respectively. This we have not mentioned in the methodology.

Serum levels of Immunological panel

The mean and standard deviation of the levels of immune panel is expressed in the table 1. Treatment with ICB03 demonstrated significant increase in CD3 and CD4 counts as compared to control. than Chyawanprash SF. Evident in Graph 1. In Sugar free Chyawanprash treated group, there was significant improvement in absolute counts of IgA, CD 3 (T cells), CD 45 and CD 4 (Helper T cells) from baseline to day 21. In group treated with ICB03, there was significant improvement in absolute counts of CD 3 (T cells), CD 45 and CD 4 (Helper T cells) and CD 19 Natural Killer Cells from baseline to day 21.

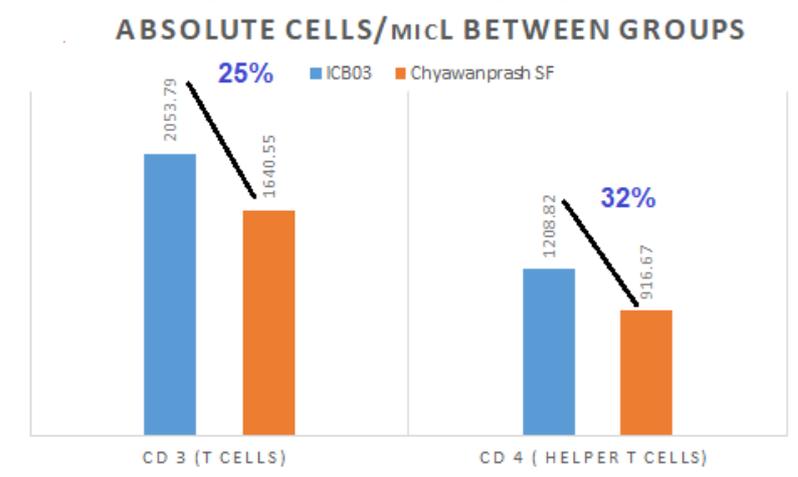
Table 1: Serum levels of Immunological panel between groups.

Parameter	Mean ± SD					P value
	Baseline		P value	Day 21		
	ICB03	Chyawanprash SF		ICB03	Chyawanprash SF	
IgG Total <i>mg/dL</i>	1484.78 (271.85)	1463.25 (360.41)	0.4221	1326.33 (320.44)	1291.67 (506.91)	0.4054
IgA Total <i>mg/dL</i>	266.94 (94.28)	252.76 (92.77)	0.3310	307.44 (97.56)	286.60 (100.99)	0.2358
IgM Total <i>mg/dL</i>	116.02 (80.77)	116.96 (85.36)	0.4868	134.68 (55.58)	119.46 (66.91)	0.2371
CD 45 absolute (Lymphocyte gated) <i>/c.mm</i>	1874.24 (583.03)	1796.66 (734.83)	0.3691	2949.98 (1148.41)	2472.38 (697.63)	0.0794
CD 3 (T cells) Absolute cells/μL	1339.61 (419.45)	1179.23 (453.42)	0.1496	2053.79 (747.22)	1640.55 (419.85)	0.0298
CD 4 (Helper T cells) Absolute cells/μL	731.09 (193.43)	672.51 (273.42)	0.2402	1208.82 (575.05)	916.67 (228.44)	0.0331

CD 8 (Suppressor T cells) Absolute cells/ μ L	600.81 (248.96)	498.49 (249.40)	0.1236	285.36 (277.14)	654.70 (270.87)	0.0716
CD 19 Natural Killer Cells cells/ μ L	190.25 (122.01)	238.33 (205.59)	0.2034	445.84 (189.10)	400.94 (289.19)	0.2959

Between groups analysis was performed by unpaired t test. Significant at $p < 0.05$

Graph 1: Changes in immunity parameters between groups



Serum levels of inflammatory markers:

In Chyawanprash SF treated group there was 69.81, 79.22 and 30.3 % decrease in serum levels of CRP, IL-6 and TNF alpha from baseline to day 21. ICB03 demonstrated 40.83 and 49.66% decrease in IL-6 and TNF alpha levels. The results are depicted in Table no. 2

Table 2: Serum levels of inflammatory markers (% decrease)

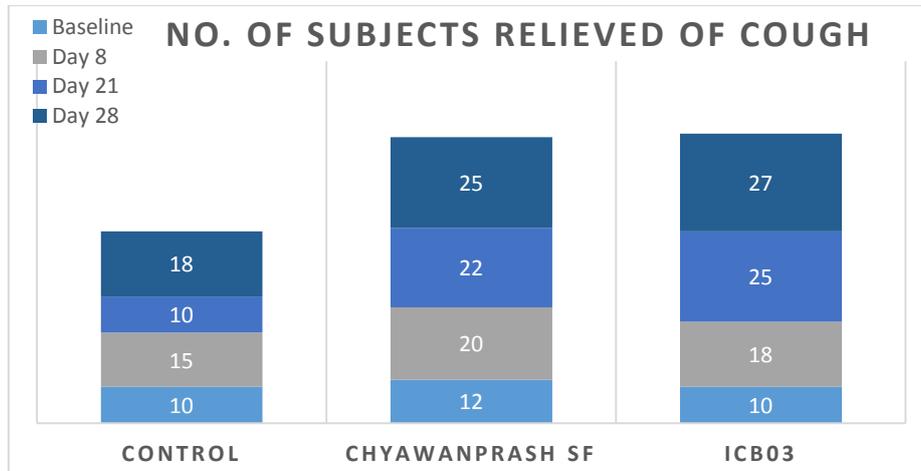
Parameter	Chyawanprash SF		% decrease	ICB03		% decrease
	Baseline	Day 21		Baseline	Day 21	
CRP- C Reactive Protein mg/L	13.15	3.97	69.81	2.7	2.93	-8.52
IL-6 (Interleukin-6) pg/mL	14.58	3.03	79.22	3.87	2.29	40.83
TNF Alpha pg/mL	8.72	6.07	30.39	10.35	5.21	49.66

Changes in severity of symptoms

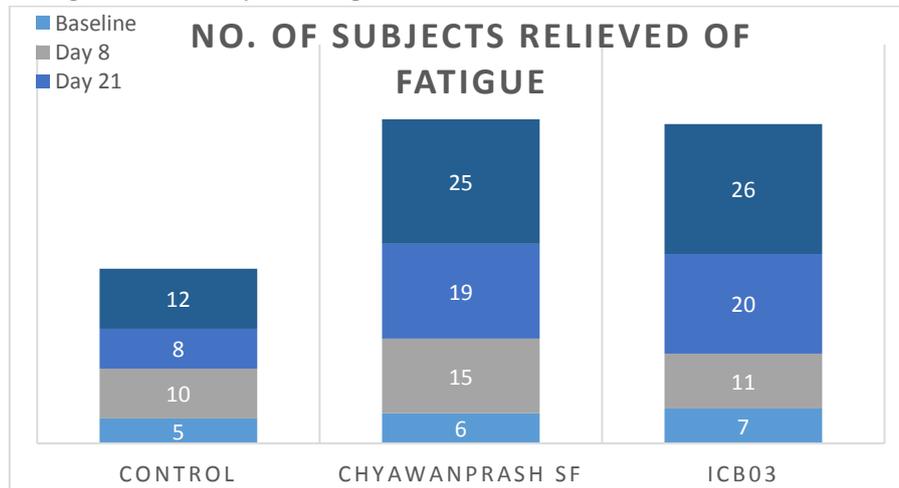
In case of all three groups the symptom representation in proportion of subjects was comparable at baseline this denotes that there was no significant difference in the symptomatology at baseline amongst groups. Gradually at day 8, 21 and 28 the subjects experiencing moderate or mild symptoms like cough, breathlessness and fatigue were getting shifted to no symptoms in all the groups. When compared between the groups Chyawanprash

SF and ICB03 treated groups produced early recovery from cough, breathlessness and fatigue than subjects only on standard of care. The results are depicted in Graph 2, 3, and 4.

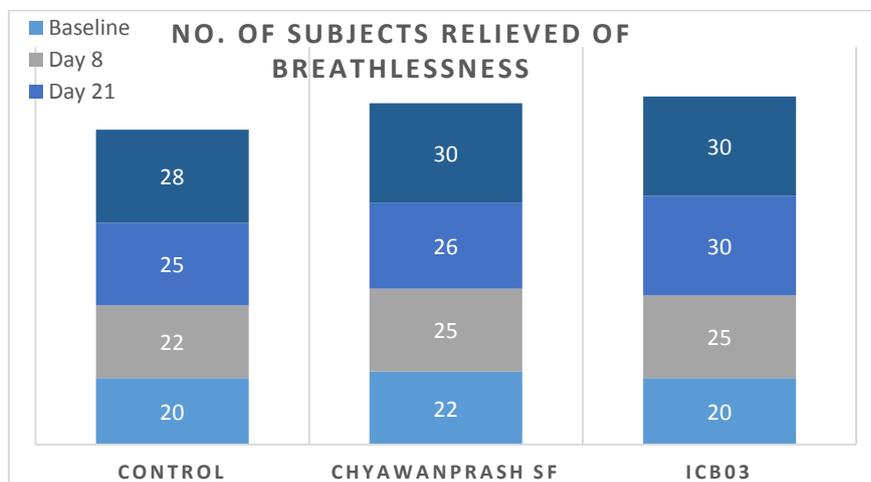
Graph 2: Changes in severity of cough



Graph 3: Changes in severity of fatigue



Graph 4: Changes in severity of breathlessness



Assessment of safety of intervention through the biochemical parameters:

The safety of intervention was assessed through the biochemical parameters like complete blood count, liver, renal function test and serum electrolyte levels. It was evident from the results depicted in tables below that there were no significant changes in the biochemical parameters from baseline to 21 days. There was no significant difference in any of the biochemical parameter after treatment with Chyawanprash SF and ICB03 in COVID 19 patients.

Compliance of the intervention

There was 100% compliance in all the subjects from the ICB03 and Chyawanprash SF treated group. This indicates excellent tolerability of ICB03 and Chyawanprash SF in COVID 19 patients with mild to moderate presentation.

Profile of adverse events

There were no adverse events except toothache, bloating, palpitations, sleeplessness and menstrual pain in 7 cases of standard group and 3 and 5 cases of ICB03 and Chyawanprash SF treated groups respectively. The complaints got resolved without rescue medication and there was no need to stop the medication in all three groups. There were no adverse events related to possible engagement of test intervention.

DISCUSSION:

In the present study group, we had patients with mean age 34.3, SD 8.9, with male predominance (Male/Female-77/23). As the study centre was designated for asymptomatic/mildly symptomatic patients who were either asymptomatic (around 30%) or had mild symptoms (around 70%). This was felt to be the fair representation of Indian scenario of clinical severity which is in accordance with the Indian data published by Ghosh, 2021 being 80% population asymptomatic.

COVID 19 infection causes respiratory tract infection & can progress to a more severe and systemic disease characterized by the Acute Respiratory Distress Syndrome (ARDS), septic shock, multi-organ failure if progressed to severe infection (15).

Clinical scenario around COVID 19 in India presents following 3 challenges- first- mass immunization and prophylaxis, second- healthcare infrastructure requirements for asymptomatic and mild patients and third- avoiding progression of disease to minimize fatalities.

Improving prognosis of disease through modulating host immunity was the basis of incorporating Ayurvedic intervention in treatment protocol of patients with mild clinical presentation to avoid their progress to moderate and severe disease. Ayurveda has foundation to modulate host immunity to correct the infection since many years.

According to the earlier study conducted, cough, breathlessness and fatigue in COVID 19 are indicative of accelerated disease progression and lung damage (16). Treatment with ICB03 and Chyawanprash SF demonstrated that around 50% of subjects were relieved of cough, shortness of breath and fatigue more effectively and in around 7 days which is short period of time than only standard of care. In 21 days around 90-100 % subjects were relieved of symptoms in ICB03 and Chyawanprash SF treatment while still some patients were

experiencing symptoms with only standard of care. Subjects with ICB03 and Chyawanprash SF treatment presented improved overall quality of life and early recoveries.

Elders and people suffering of diabetes, hypertension and cardiovascular diseases have already a state of oxidative stress, viral infection will upsurge this stress, giving one possible explanation of the severity of COVID-19 in these comorbid categories of patients (17). In the present study, there were around 30% subjects with comorbidity in each of three groups. Treatment with ICB03 and Chyawanprash SF proved to be beneficial in comorbid patients improving their symptoms and overall health. Chyawanprash in its sugar free formula was safe in subjects with diabetes as well; it did not alter the blood sugar levels.

Chyawanprash is the ancient formulation of Ayurveda and a blend of Amla with immunity improving herbs like *Tinosporacardifolia*, *Withaniasomnifera* etc. (18,19) The herbs and the bioactive obtained from the herbal source such as *Curcuma longa*, *Andrographis paniculata*, Amla, *Glycyrrhiza glabra* are excellent antioxidants (20). The activity of improvement in symptoms and clinical recovery may attribute to the antioxidant activity of ingredients of ICB03 and Chyawanprash SF. *Glycyrrhiza glabra* is proven antitussive and *Terminalia bellirica* is bronchodilator (21, 22), the faster recovery of subject's form cough and breathlessness could be attributed to these ingredients present in ICB03 and Chyawanprash SF (23).

Chyawanprash SF demonstrated significant improvement in CD3, 4 and 45 counts and ICB03 illustrated significant improvement in CD3, 4, 45 counts along with CD19 i.e., natural killer cells.

It is well researched fact that decreased levels of the total CD3+CD4+ T cells counts were linked to a critical evolution of COVID-19 patients with bilateral pneumonia and requirement of aggressive treatments with corticosteroids or IL-6 inhibitors (24).

There are two confounding parameters that may describe the immune dysregulation in COVID-19. First is an overproduction of pro-inflammatory cytokines by monocytes, and the second is a CD4 lymphopenia and subsequently B cell lymphopenia (25). The cellular immune response activation (lymphocytic) has been shown to be the most effective against clearing viral infections (27). Covid 19 is characterized by the delayed development of the adaptive immune response and delayed virus clearance in severe stages (26). In reference to the present study, both Ayurvedic interventions present merit of activation of lymphocyte gated immune response and thus shifting paradigm towards immune regulation and avoiding monocyte induced cytokine storm. Similar observation supported the fact of no one from the Ayurvedic intervention treated group showed disease progression.

Earlier research suggested a reduction in NK cell number and function, resulting in reduced viral clearance, and unrestrained elevation of tissue-damaging cytokines. SARS-CoV-2 infection tilts the immune response towards cytokine response. Restoration of NK cell activity and count can prove beneficial in attaining the correct and delicate immune balance for faster clinical recovery (28). In the present study, ICB03 improved natural killer cell counts significantly from baseline to end of study, suggesting immunomodulatory activity.

Inflammatory markers like CRP, IL-6 and TNF alpha are thought to be associated with cytokine storm, lung injury and progression of COVID 19 disease. Elevated markers further abridged probabilities of recovery (29). In the present study, Chyawanprash SF and ICB 03 demonstrated potential anti-inflammatory activity. Ayurvedic intervention like

Chyawanprash SF and ICB03 can be a potential choice to be incorporated in the COVID 19 protocol as it will help to modulate immunity as well as reduce the expression of inflammatory mediators.

Lung lesions and CRP levels is a well correlated equation (31). Around 70% reduction in elevated CRP levels in Chyawanprash SF treated group may act as surrogate marker of improved lung pathology. Higher lung inflammation may result in reduced lung capacity through scarring thus reduced Quality of Life (QoL) post COVID 19 infection. So, interventions which are directed to reduce inflammation can help restoring lung and vital organ function resulting in faster clinical recovery and better QoL. The beneficial effects of Chyawanprash SF and ICB03 in reducing inflammation can be extrapolated to improved lung health in COVID 19 patients.

Similar to IL-6 and CRP, raised levels of TNF- α has also correlation to severity of COVID 19 disease (32). It can be inferred from fact that out of study intervention, both the Ayurvedic medicines Chyawanprash SF and ICB03 had potential to mitigate three risk factors in COVID 19 such as raised levels of CRP, IL-6 and TNF- α .

Ayurvedic interventions Chyawanprash SF and ICB03 present possible potential in the treatment of COVID 19 through their antioxidant, anti-inflammatory, immunomodulatory action. These interventions possess potential of vital organ protection and clinical recovery hand in hand.

Both interventions ICB03 and Chyawanprash SF are found safe to be used in the management of COVID 19 as evident by no changes in biochemical parameters like CBC, LFT, KFT and serum electrolytes. There were no adverse events related to study interventions.

CONCLUSION

The outcome of this study was reduction in the time to recovery in clinical symptoms, increased CD3, CD4 and natural killer cells and decreased in elevated serum levels of CRP, IL-6 and tumour necrosis factor alpha (TNF- α). This study confirms safety of Chyawanprash SF and ICB03 in treatment of COVID 19 with no evident adverse effects as well as excellent tolerability. Another outcome of the trial is to build confidence in the stakeholders of Ayurveda research and providing them guiding light towards clinical guidelines over use of Ayurveda intervention in COVID 19. Treatment with ICB03 and Chyawanprash SF swiftly reduced in clinical symptoms like cough, fatigue and breathlessness improving patient QoL. Immunomodulatory activity offered by treatment of ICB03 and Chyawanprash SF through increased CD3, 4, 45 and natural killer cell counts can be the basis of faster viral irradiation. Anti-inflammatory activity of these interventions can contribute to halt progression of disease and to minimize lung involvement. Thus, it can be concluded from the present study that ICB03 and Chyawanprash SF are safe and effective in treatment of COVID 19 along with standard of care.

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CONFLICTS OF INTERESTS:

The authors state that there were no conflicts of interest during the process of study.

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