Original Article

Clinical evaluation of *Chyawanprash* as a preventive measure during the COVID-19 pandemic: An open-label, multicentric, randomized, comparative, prospective, and interventional community-based clinical study on healthy individuals

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Abstract

Background: *Chyawanprash* is a classical Ayurveda polyherbal formulation that has proven immunomodulatory potential. **Aim:** The present clinical study was conducted to evaluate *Chyawanprash* for prophylaxis of COVID-19 infection. Materials & Methods: It was an Open-label, Multicentric, Randomized, Comparative, Prospective, and Interventional Community-based Clinical Study. The study was conducted at five sites across Maharashtra, Gujarat, and Rajasthan between May 2020 and November 2020. **Materials and Methods:** A total of 771 subjects were screened in the study; of whom, 721 subjects were randomized into two groups. Subjects in the DCP group who fell into the category of 13 years to 70 years were given *Chyawanprash* as a study intervention to be taken in a dose of one teaspoonful (approx. 12g) twice daily and children aged 5 to 12 years were given ½ teaspoonful (approx. 6g) twice daily followed by a cup of milk (approx. 200mL). Subjects in the control group were advised to consume one cup of milk (approx. 200mL) twice daily. The incidence of COVID-19 was assessed by reverse transcription polymerase chain reaction (RT-PCR)/antigen testing, which was conducted as per applicable guidelines and the severity of infection was assessed by using the World Health Organization (WHO) ordinal scale. The incidence and severity of non-COVID-19 infections was also assessed during the intervention period of 90 days. **Results:** Overall, 696 subjects completed the study, of whom 351 subjects were in the Chyawanprash (DCP) group and 345 were in the control group. In the DCP group, out of the 351 subjects who had completed the study, 42 were tested with RT-PCR/antigen and one subject was found to be positive for COVID-19. In the control group, out of the 345 subjects, 28 were tested with RT-PCR/Antigen and eight subjects were found to be positive for COVD-19. In the DCP group, the incidence was statistically significant lesser as compared with the control group. A total of 43 subjects in the control group and 41 subjects in the DCP group had symptoms of Influenza Like Illness (ILI). The DCP group also showed a statistically significant improvement in quality of life (QoL), as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) when compared with the control group. **Conclusion:** The outcome of the present study suggests and supports the prophylaxis potential of *Chyawanprash* as one of the preventive remedies for COVID-19 as recommended by the AYUSH fraternity. The beneficial effects may be due to the synergistic effects of the potent herbs that are known to have immune-boosting effects in healthy individuals.

Keywords: *Chyawanprash*, COVID-19, immunity, RT-PCR, WHO ordinal scale

Introduction

In the current global health scenario, the SARS-CoV-2-associated pandemic COVID-19 is a matter of concern:

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Preventive remedies are expected to play a crucial role till specific curative remedies are available for the common public of India; a plausible plan of action for Ayurveda preventive remedies has been recommended. In this context, empirical and traditional herbal remedies can be made more authentic by revalidating the safety and broad-spectrum benefits of the potential herbal candidates for prevention and treatment protocols.

Ayurveda classics describe epidemics and pandemics as "*Janapadodwansa*," where a large community is afflicted with a disease leading to high morbidity and mortality. Ayurveda believes that individuals defer in physical and physiological makeup, immune response, food habits, psychological makeup, adaptations, mental strength, etc.; still, they can get affected with the disease owing to the vitiation of factors that are common to all, those who inhabit a common environment and community. These factors lead to the simultaneous manifestation of disease in masses, whereby all the inhabitants have the same symptoms, leading to widespread manifestation in the community. The factors that are common to all the individuals in a community include air, water, land, and season.[1] Ayurveda mentions different modes of transmission of communicable diseases, such as physical contact, expired air, eating with others from the same plate, sharing a bed, using others' clothes, garlands etc., leading to infectious diseases spreading from person to person. These diseases include skin diseases (*Kuṣṭha*), fever (*Jvara*), pulmonary tuberculosis (*Soṣa*), and conjunctivitis (*Netrabhisyanda*), among others, which are caused by direct contact and respiratory routes.[2]

Ayurveda also describes *Agantuja Vyadhi* (infectious disease), which is caused due to *Krimi*/*Bhuta* (microorganism) and *Visha* (toxins). These factors, on entering the human body, cause an imbalance in the *Dosas*, *Agni,* and *Dhatu*s; result in *Srotas Dusti*; and manifest in the form of a disease.[3] Apart from the remedies for the symptoms of the disease during such an outbreak, Ayurveda texts also strongly advise the use of *Rasayana* medicines to boost the immune system toward overcoming the illness. The group of plants in the *Rasayana* group generally possesses strong antioxidant activity. The cellular damage and decreased immunity induced by free radicals has been implicated in several disorders and diseases.[4] In Ayurveda, the use of *Rasayana* is in regular practice for mainly combating immunity and age-related disorders and diseases, as many of the components, that is, naturally occurring antioxidant rich herbs of *Rasayana*, are known for their free-radical scavenging and immunomodulatory activity, which plays a vital role in combating these conditions. Modern pharmacology interprets *Rasayana* as a product having antioxidant, immunomodulatory, anti-stress, antiaging, and nootropic properties, which promote good health.

Earlier studies on *Chyawanprash* show that the product has been tested as safe and effective in both promoting immunity and protecting one from common respiratory infections, such as a common cold, sore throat, rhinitis, etc. It is known to have antibacterial, anti-allergic, and immunostimulatory effects according to various preclinical and clinical studies. It has been found to be useful in treating pulmonary infections,[5] respiratory damage due to particulate matter in polluted air; in promoting growth and general well-being in children; and in curing various infections and allergies.

Hence, *Chyawanprash* was considered to evaluate its prophylactic potential in the prevention of COVID-19 infection in healthy subjects.

Materials and Methods

A randomized, controlled, prospective, and multicentric community-based clinical study was conducted in healthy male and female volunteers for a period of 90 days. A total of 771 subjects were screened in the study; out of these, 50 were screen failures, as they did not meet the inclusion criteria. A total of 721 subjects (362 subjects in the DCP group and 359 subjects in the control group) were randomized. However, 25 subjects (11 in the DCP group and 14 in the control group) were considered as dropouts and were not considered for efficacy evaluation. A total of 696 subjects (351 subjects in the DCP group and 345 subjects in the control group) were considered as completers or efficacy-evaluable cases at the end of the study.

The study was carried out at the study sites and at a community level. Screening of subjects was done after receiving approval from the Institutional Ethics Committee (IEC) of the respective sites and registration of the study at the Clinical Trial Registry of India (CTRI) (Reg. No. CTRI/2020/05/024981, dated 2 May 2020).

The study was conducted in the Western part of India, where the incidence was higher during the study period. Five Ayurveda institutions across three states were selected for the study, namely (1) National Institute of Ayurveda, Jaipur, Rajasthan; (2) Parul Ayurveda Hospital, Parul University, Vadodara, Gujarat; (3) MAM's SS Ayurveda Mahavidyalaya and Sane Guruji Arogya Kendra, Pune, Maharashtra; (4) R A Podar Medical College (Ayu) and M.A. Podar Hospital Worli, Mumbai, Maharashtra; and (5) Khemdas Ayurved Hospital, Vadodra, Gujarat.

Study Objective and Outcomes

The primary objective of the study was to evaluate *Chyawanprash* as a preventive measure for COVID-19 and other non-COVID-19 infections in a healthy population. The primary outcome was a comparative assessment of the incidence of COVID-19 and other non-COVID-19

infections in subjects taking DCP and those not taking it over a period of three months (90 days).

Secondary outcomes included a comparative assessment of the severity of COVID-19 using the WHO ordinal scale,[6] the number of subjects requiring hospitalization, the number of days of hospitalization, the number of subjects requiring ICU admission, the number of subjects requiring ventilator support and mortality rate, the incidence and severity of other allergy-related health problems such as cough, sneezing, rhinitis, sore throat etc., changes in the QoL evaluated on the Q-LES-Q-SF, and global assessment of efficacy and safety.

Inclusion and Exclusion Criteria

Healthy male or female subjects in the age group of 5 years to 70 years (both inclusive) were included in the study. Healthy individuals were considered as those who did not have any acute medical condition or chronic medical/surgical condition that required both immediate and continuous medical monitoring and treatment. Only the subjects who were ready to provide written informed consent and who were ready to willingly participate and follow the protocol requirements of the clinical study were included.

Pregnant and lactating females, subjects who had been confirmed to have COVID-19 and had been isolated for its treatment, or those who had recently suffered and recovered from COVID-19 were excluded from the study. Other exclusion criteria were: Diabetes Mellitus; any medical or surgical condition that would require immediate medical or surgical intervention at the time of screening; an immune-compromised status due to human immunodeficiency virus (HIV), hepatitis, tuberculosis, cancer, etc.; ongoing steroid treatment and/or any kind of immunosuppressive therapy; currently participating or having participated in any other study three months before screening in the present study; past history of allergy to *Chyawanprash*-like products; and other conditions, which, in the opinion of the investigators, made the patient unsuitable for enrollment or could interfere in adherence to the study protocol.

Investigational Product

Chyawanprash is a well-known Ayurveda classical formulation that has been in use since ancient times. Chyawan was an aged sage who first used this preparation to regain vitality and longevity. *Prash* means a product or foodstuff that is suitable for consumption.

The study product *Chyawanprash* (DCP) is a polyherbal traditional Ayurveda medicine possessing the following ingredients: *Bilva (Aegle marmelos), Agnimantha (Premna integrifolia), Syonaka (Oroxylum indicum), Patala (Stereospermum suaveolens), Gambhari (Gmelina arborea), Shalaprani (Desmodium gangeticum), Prishniparni (Uraria picta), Brihati (Solanum indicum), Kantakari (Solanum xanthocarpum), Gokshura (Tribulus terrestris), Bala (Sida cordifolia), Mudgaparni (Phaseolus trilobus), Mashaparni (Teramnus labialis), Karkatshringi (Pistacia integerrima), Tamalaki (Phyllanthus niruri), Draksha (Vitis vinifera), Jivanti (Leptadenia reticulata), Pushkara (Inula recemosa), Haritaki (Terminalia chebula), Guduchi (Tinospora cordifolia), Varahi (Dioscorea bulbifera), Vidari (Pueraria tuberosa), Karchura (Curcuma zedoaria), Musta (Cyperus rotundus), Punarnava (Boerhaavia diffusa), Shatavari (Asparagus racemosus), Utpala (Nymphaea stellata), Vasa (Adhatoda vasica), Ashwagandha (Withania somnifera), Kakanasika (Maritima annua), Yasti (Glycyrrhiza glabra), Amalaki (Emblica officinalis), Chandan Saar (Santalum album), Nagakesara (Mesua ferrea), Pippali (Piper longum), Tvak (Cinnamomum zeylanicum), Tvakpatra (Cinnamomum tamala), Lavanga (Syzygium aromaticum), Sukshmaila (Elettaria cardamomum), Abhraka Bhasma, Akarakarabha (Anacyclus pyrethrum), Muktashukti pishti, Kumkuma (Crocus sativus), Vamsha (Bambusa bambos)* along with *Til tail (Sesamum indicum), Ghrit,* Crystal Sugar *(Sharkara)*, and *Honey (Madhu)* along with preservatives and excipients. The study product was provided by Dabur India Limited. The product is prepared as per the classical reference of the book *Rasatantra Sara Va Siddha Prayog Sangraha*.[7]

Healthy male/female subjects in the age group of 5 years to 70 years (both inclusive) were screened for eligibility criteria. On screening/ baseline visit, informed consent (e-consent/written consent) was obtained from subjects or from children's parent/legally acceptable representative (LAR) for their participation in the study. Assent was obtained from children between 13 and 18 years of age along with consent (e-consent/written consent) from their parent(s)/LAR. An assessment of the inclusion and exclusion criteria was done.

Subjects who met all the inclusion/exclusion criteria were recruited in the study. After clinical assessment by the investigator, subjects were randomized as per a computer-generated randomization list to either Group A or Group B. Subjects from Group A in the age group of 13 years to 70 years were provided with *Chyawanprash* (DCP) and advised to take DCP in a dose of one teaspoonful (approx. 12 g) twice daily; children in the age group of 5 to 12 years were given ½ teaspoonful (6 g) twice daily followed by a cup of milk (approx. 200 mL) for 90 days.

Subjects in Group B were not provided with any study product and were asked to take one cup of milk twice daily (approx. 200 mL) for 90 days. Subjects in both the groups were advised to follow their normal routine and diet that they had been already following. All participating subjects were asked to follow COVID-19 related guidelines (for prevention and containment of

infection) provided by the local health authorities and other government agencies from time to time. Subjects were asked to visit the study site on day 45 and day 90 for clinical assessment, including QoL assessment. Telephonic follow-up to confirm health status and assess immunity/infection/adverse event (AE), including COVID-19, was conducted by the study team on day 15, day 30, day 60, and day 75.

The study data for all the study participants were captured in an Electronic Case Record Form (e-CRF) prepared as per the 21 CFR compliant, Electronic Data Capturing (EDC) system. All the requirements of the standards of safety, quality, and confidentiality of the subject data were followed for data collection.

During the study period, subjects who experienced any of the COVID-19 related symptoms (such as fever, cough, sore throat, weakness, difficulty in breathing, etc.) were advised to follow guidelines regarding testing, medication, quarantine, and any care related to COVID-19 infection issued by the Government of India/state health authorities/ local health authorities as and when available from time to time.

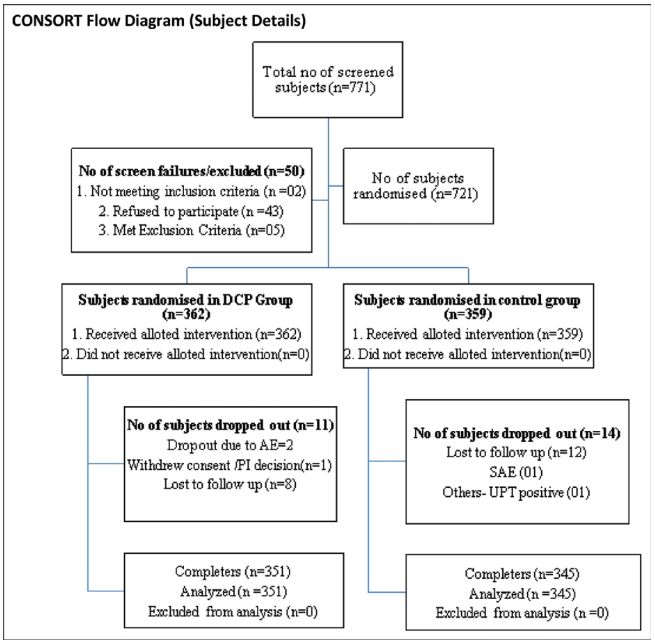
Subjects were asked to follow all general preventive measures such as hand hygiene, wearing masks, social distancing etc. as issued by the government and health authorities. All study-related personnel, including the investigators and all study staff, were trained on the study protocol as well as COVID-19 guidelines.

Statistical Analysis

The conclusion and the final results were derived from the study data generated and collected and that were put to statistical analysis. Demographic data were presented in tables and graphs. The data obtained in the study were subjected to tests of significance. GraphPad InStat Version 3.6 (www.graphpad.com) software was used for the statistical analysis of data. For intergroup comparison, an unpaired t-test was applied to continuous data. For discrete data (counted facts), a nonparametric test, that is, χ^2 test of independence, was applied. A *P*-value of <0.05 was considered significant.

Observation and Results

CONSORT Flow Diagram (Subject Details)



A total of 696 subjects completed the study. The demographic details of the subjects assessed are given in Table 1.

Primary Outcomes

Comparative assessment of the incidence of COVID-19 (Overall symptomatic and asymptomatic subjects)

A total of 70 (10.05%) subjects (42 in the DCP group and 28 in the control group) were tested for COVID-19 by RT-PCR/antigen test; out of these, nine (12.85%) subjects (one in the DCP group and eight in the control group)

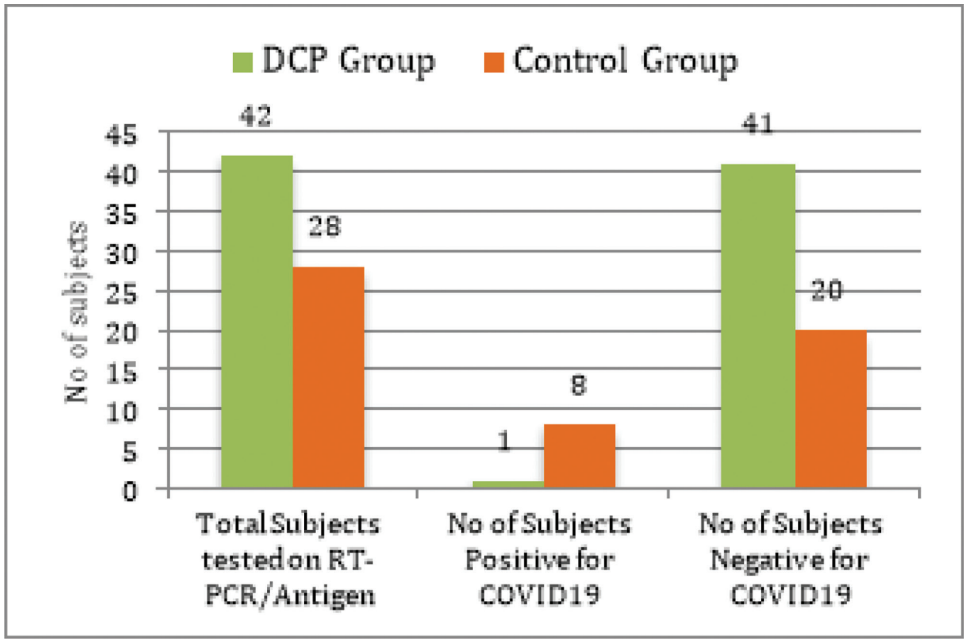
Table 1: Demographic data

Parameters	DCP group (n = 351)	Control group (n = 345)
Age (in years), mean ± SD	33.52 ± 12.46	31.73 ± 12.34
Gender-wise distribution		
Male	194 (55.27%)	186 (53.91%)
Female	157 (44.72%)	159 (46.08%)
Occupation-wise distribution		
Housewives	46 (13.10%)	49 (14.20%)
Students	76 (21.65%)	92 (26.66%)
Healthcare workers (doctors, nurses etc.)	66 (18.80%)	67 (19.42%)
Security staff/police	14 (3.98%)	6 (1.73%)
Sanitation/cleaning staff	11 (3.13%)	8 (2.31%)
Others	138 (39.31%)	123 (35.65%)
Total	351 (100%)	345 (100%)

tested positive for COVID-19, and 61 (87.15%) subjects (41 in the DCP group and 20 in the control group) tested negative for COVID-19. When a comparison was drawn between the groups, a statistically significantly ($P < 0.05$) lesser number of subjects were found to be infected with COVID-19 in the DCP group as compared with subjects in the control group [Graph 1]. The result shows that the incidence of COVID-19 infection in the *Chyawanprash* group was 12 times lesser in comparison to the control group.

A total of 93 subjects (42 in the DCP group and 51 in the control group) had symptoms such as fever, sore throat, cough, cold, body ache etc.; out of these, RT-PCR/antigen test was done in 19 (20.43%) subjects (eight in the DCP group and 11 in the control group). Of these, nine (47.37%) subjects (one in the DCP group and eight in the control group) tested positive, whereas 10 (52.63%) subjects (seven in the DCP group and three in the control group) tested negative for COVID-19. When compared between the groups, a statistically significant ($P < 0.05$) lesser number of subjects having COVID-19 related symptoms tested positive for COVID-19 in the DCP group as compared with subjects in the control group [Table 2].

The Severity of Infection: The WHO ordinal scale for rating the severity of COVID-19 was used in subjects diagnosed with COVID-19. The initial score (at the time of diagnosis) of one subject in the DCP group was "3," which improved to "0" as the subject completely recovered from COVID-19. In the control group, out of the eight subjects diagnosed with COVID-19 infection, four subjects had a score of "3" whereas the other four subjects had a score of "2" at the time of diagnosis. During the course of infection (COVID-19), the score improved to "0" for seven subjects whereas it worsened to "8" for one subject in the control group. This summed up to a score of "0" in the DCP group and a score of "8" in the control group at the end of the study. Table 3 shows the summary of the severity of COVID-19 infection in both the groups. The assessment between the groups shows that in the *Chyawanprash* group, there was six times lesser severity of COVID-19 infection when compared with subjects in the control group.



Graph 1: Comparative assessment of number of subjects tested for RT-PCR/antigen

Table 2: RT-PCR/antigen testing in symptomatic subjects

Group	Total no. of symptomatic patients	Symptomatic participants in whom RT-PCR was done	Symptomatic participants with positive RT-PCR	Symptomatic participants with negative RT-PCR
Total	93	19 (20.43%)	09 (47.37%)	10 (52.63%)
DCP Group	42	8 (19.04%)	01 (12.50%)	07 (87.50%)
Control Group	51	11 (21.56%)	08 (72.72%)	03 (27.28%)
		$P = 0.5157$ (NS)	$P = 0.0331$ (S)	

RT-PCR = reverse transcription polymerase chain reaction; NS = not significant; S = significant

Table 3: Assessment of severity as per the WHO ordinal scale

Study group	Individual scores at time of diagnosis	Total score at the time of diagnosis	Individual scores during course of the study	Total score during course of the study	Individual scores at study completion	Total score at the end of the study
DCP group	1 Subject's score = 3	3	1 Subject's score =0	0	1 Subject's score =0	0
Control group	4 Subjects' score= 3 4 Subjects' score =2	20	7 Subjects' score = 0 1 Subject's score =8	8	7 Subjects' score = 0 1 Subject's score =8	8

WHO = World Health Organization

Table 4: Assessment of episodes of Non-COVID-19-related symptoms (ILI)

Parameter	Total	DCP group	Control group	*P* value between the groups
No. of episodes of illness related to infection/immunity (non-COVID-19)	164	66 (40.24%)	98 (59.75%)	0.001 (S)

ILI = influenza like illness; S = significant

Hospitalization of Subjects

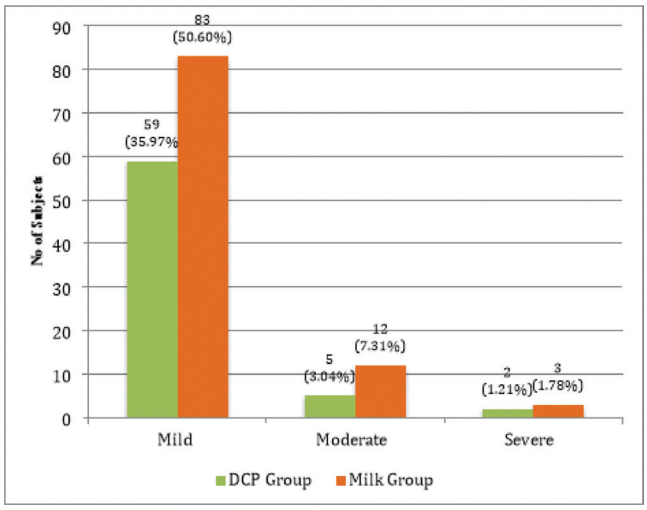
A total of five subjects required hospitalization during the study period, of whom one was in the DCP group and four were in the control group. The subject in the DCP group was hospitalized for four days whereas the total number of days of hospitalization of four subjects in the control group was 43 days, with an average of 10.75 days per subject. None of the subjects required ICU admission or ventilator support, and there was no mortality in the DCP group. In the control group, one subject required ICU admission, and none required ventilator support. The subject requiring ICU admission died due to COVID-19.

Assessment of Non-COVID-19-Related Symptoms

A total of 164 episodes of illness not related to COVID-19 were observed during the study period. Of these, 66 episodes were observed in subjects in the DCP group (40.24%). Results show that the *Chyawanprash* group had 48.48% fewer chances of incidence of ILI symptoms in comparison to the control group.

Out of 66 episodes of illness related to infection/immunity (Non-COVID-19), reported in the DCP group, 59 (89.39%) episodes were mild, five (7.57%) episodes were moderate, and 2 (3.03%) episodes were severe in nature. In the control group, 98 (59.75%) episodes of illness related to infection/immunity (Non-COVID-19) were observed. Out of these, 83 (84.69%) episodes were mild, 12 (12.24%) episodes were moderate, and three (3.06%) episodes were severe in nature [Table 4].

When compared between the groups, a statistically significant ($P < 0.05$) lesser number of episodes were observed in the DCP group as compared with the control group. However, when assessed between the groups, no statistically significant difference was observed ($P > 0.05$) with respect to the severity of episodes, although a higher number of subjects in the control arm had severe to moderate episodes of infections as compared with the DCP group [Graph 2 and Table 5].



Graph 2: Assessment of severity of episodes of Non-COVID 19 infections

Table 5: Assessment of severity of episodes of non-COVID 19 infections

Severity	DCP group	Control group	*P* value between the groups
Total episodes	66 (100%)	98 (100%)	
Mild	59 (89.39%)	83 (84.69%)	0.6281
Moderate	5 (7.57%)	12 (12.24%)	
Severe	2 (3.03%)	3 (3.06%)	

Assessment of incidence of allergies: A total of six episodes of allergy-related health problems such as rhinitis, sneezing, etc. were reported during the study period. Of these, two (33.33%) episodes were reported in the DCP group whereas four (66.66%) episodes were reported in the control group. When compared between the groups, no significant difference was observed ($P > 0.05$). The differential diagnosis of these episodes from infection-related episodes was done by the investigator based on the subjects' history.

Assessment of Changes in QoL Evaluated on Q-LES-Q-SF

In the DCP group, the QoL score was 66.79 ± 14.75 at the baseline visit, which significantly improved to 70.83 ± 13.57 ($P < 0.001$) at the end of the study. In the control group, the QoL score was 66.52 ±13.60 at the baseline visit, which showed a significant worsening ($P > 0.001$) at the end of the study and was 61.48 ± 12.33. On analysis between the groups, a statistically significant improvement ($P < 0.001$) in QoL was observed in the DCP group when compared with the control group [Table 6, Graph 3]. It may be inferred that the QoL in subjects using *Chyawanprash* was up to 2.25 times better than subjects in the control group.

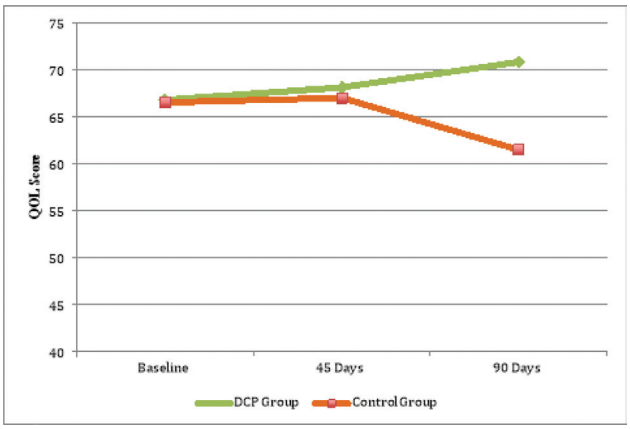
Global Assessment of Efficacy and Safety

Assessment by physician

As per the physician's assessment for overall change, 277 (78.90%) subjects showed minimal to very much improvement whereas 40 (11.39%) subjects reported no change in the DCP group. Overall, 34 (9.67%) subjects reported minimum to very much worsening in this group. In the control group, 149 (43.18%) subjects showed minimal to very much improvement whereas 161 (46.66%) subjects reported no change and 35 (10.12%) subjects reported minimum to very much worsening.

Subject self-assessment

As per the subject's assessment for overall change, 278 (79.19%) subjects showed minimal to very much improvement whereas 38 (10.82%) subjects reported no change in the DCP group. Overall, 34 (9.67%) subjects reported minimum to very much worsening in this group. In the control group, 158 (45.79%) subjects showed minimal to very much improvement whereas 151 (43.76%) subjects reported no change and 36 (10.41%) subjects reported minimum to very much worsening.



Graph 3: Assessment of changes in qality of life evaluated on Q-LES-Q-SF

Global Safety Assessment of DCP as per Physician and Participant

Subjects in the DCP group were assessed for overall safety assessment by both the physician and the participant. As per the global assessment of overall safety assessed by the physician in the 351 subjects in the DCP group, excellent overall safety was observed in 223 (63.53%) subjects, good overall safety was observed in 113 (32.19%) subjects, and fair overall safety was observed in 15 (4.27%) subjects. Also, as per the subject's assessment, excellent overall safety was observed in 226 (64.38%) subjects, good overall safety was observed in 110 (31.33%) subjects, and fair overall safety was observed in 15 (4.27%) subjects.

Safety Assessment by Evaluation of Occurrence of AE/SAE

All AEs, which were not related to infection or allergy, were separately recorded as AE in both groups. A total of 106 episodes of AE were recorded in the study, of which 52 were in the DCP group and 54 were in the control group. The AEs in the DCP group were primarily assessed to be not related to the consumption of DCP, except only two AEs that were assessed to be possibly related: One was pruritus ani, and the other was mild skin allergy. Both these AEs were mild in nature, and they resolved with symptomatic treatment. There were a total of six serious adverse events (SAE): One in the DCP group and five in the control group were observed during the study period. All the SAEs were found to be not related to the study product.

Discussion

The novel coronavirus (SARS-CoV-2), originated from bats, is a zoonotic virus that infects humans. Coronaviruses are single-stranded positive-sense RNA viruses that are encapsulated within a membrane envelope. Coronaviruses have genomic material with a single-stranded positive sense (+ss) RNA as messenger RNA (mRNA) in the infection cycle.[8]

Table 6: Assessment of changes in QoL evaluated on Q-LES-Q-SF

Group	Baseline score	Day 45	*P*-value from baseline	Day 90	*P*-value from baseline
DCP group	66.79 ± 14.75	68.12 ± 14.72	<0.001	70.83 ± 13.57	<0.001
Control group	66.52 ± 13.60	67.00 ± 13.42	0.056	61.48 ± 12.33	<0.001 (decrease)
P-value between the groups	0.401	0.0125			<0.001

Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form

Even though the common symptoms of the coronavirus infections are similar, each coronavirus infection includes unique symptoms. The general symptoms of human coronaviruses are fever, cough, muscle pain, weakness, respiratory symptoms, and shortness of breath. These common symptoms can be changed depending on the patient's immune response; however, asymptomatic people do not develop any symptoms.[9]

The preventive strategy as per modern medical science is basically focused on the development of various vaccines.[10] In such a situation where the development of a new vaccine has its own challenges with regard to information on the virus available and the time required to develop the vaccine, herbal medicine has a major role to play in alleviating the chances of infection and in improving the nonspecific immunity so as to reduce the chances of the incidence and severity of the infection.

Hence, there were guidelines by the Indian government to make the best judicial use of the traditional knowledge in Ayurveda and other herbal medicinal systems for the benefit of the common man.[11]

The *Rasayana* branch of Ayurveda is especially dealing with the methods and formulations for rejuvenation, regeneration, immunomodulation, and healthy aging.[12,13] Hence, *Rasayana* therapy may have direct relevance to the prophylaxis and management of SARS-COV-2 infection. Many herbs and formulations used in *Rasayana* therapy have been found to be effective in the immunomodulation and restoration of the immune status of the body.[14]

In this regard, *Chyawanprash*, which is known for improving immunity and used traditionally in Indian households, was also mentioned as one of the preventive remedies for COVID-19 infection. The pharmaceutical designing of the *Chyawanprash* in ancient texts is such that it is used as both a preventive and health-promoting formula. Such formulas are called as *Rasayana* formulae in Ayurveda and these are prescribed to be used for a longer duration to gain optimum benefits. *Chyawanaprash* has been studied extensively for its safety by preclinical safety studies, including acute dose oral toxicity studies, 28-day and 90-day oral toxicity studies, and it has been found to be safe for oral consumption. This only reiterates the safety of the age-old formulation.[15]

Chyawanprash has also been studied for its effects on various immunological markers in preclinical models. It has shown antibacterial activity in hydrolyzed chloroform extract form. This may be attributed to the presence of some aglycones of glycosides present in different constituents of plant formulation. The study on bacteria *Staph. aureus* and *E.coli* shows the possible protection from the ill effects of unhygienic food. The anti-allergic effects of *Chyawanprash* were studied in a preclinical model, wherein it was observed that pretreatment with *Chyawanprash* kept plasma histamine levels almost to baseline and led to a significant suppression of plasma histamine release at all time points when rats were challenged with allergen; however, in the control group, it rose significantly. This effect is indicative of the potential anti-allergic activity of *Chyawanprash*.[15] In another study, the potential inhibitory activity against ovalbumin-induced IgE release suggests the anti-allergic activity of *Chyawanprash*.[16]

In vitro immunomodulatory activity of *Chyawanprash* using Natural Killer (NK) cells showed marked enhancement of NK cells' activity mediated by specific lysis of target murine cells. Treatment with *Chyawanprash* resulted in enhanced target cell killing when compared with control cells, which suggest potential immunostimulatory activity. In another study where its activity on dendritic cells was studied, a dose-dependent maturation of dendritic cells was seen as indicative of immunomodulatory activity. In the study, *Chyawanprash* treatment also resulted in increased levels of various cytokines secreted by dendritic cells, as compared with the control.[15]

A study conducted to evaluate the immunomodulatory activity of *Chyawanprash* using phagocytosis assays employing macrophages resulted in a marked enhancement of phagocytic activity as compared with the controls.[17] *Chyawanprash* has also been studied for its potential benefits in protecting one from the harmful effects of pollution in in vivo models. It was evidenced by the inhibition of inflammatory cytokines (BALF: TNF a, IFN-g, IL-7, IL-6 and lung: TNFa, Histamine, and IL-6), chemokines (Lung: MMP-9), inflammatory cell infiltration (Cell counts in BALF), and histopathology in an experimental mice model.[18]

Clinical studies conducted with *Chyawanprash* also validate its effects in promoting immunity among people of different age groups. In a pilot clinical study conducted on 40 adult volunteers, *Chyawanprash* was helpful in decreasing the elevated levels of IgE antibodies. Maximum decrease was found in the allergic and normal group. *Chyawanprash* also improved the QoL in patients with recurrent cough and cold. In a study conducted on 177 subjects for the beneficial effects of *Chyawanprash* during seasonal variations throughout the year, *Chyawanprash* improved hemoglobin and the effect was consistent, irrespective of the season of its consumption. It also decreased serum cortisol levels, a common marker of stress.[19] In another multicentric study conducted on 707 school going children for six months, *Chyawanprash* showed better percentage improvement in energy levels, physical fitness, strength, stamina, and QOL.[20]

In the current study conducted on 721 healthy volunteers, the demographic data of subjects with regard to age, gender, and profession were equally distributed between the groups. Subjects in the *Chyawanaprash* group had a

lesser incidence of COVID-19 infection as compared with the control group.

The primary and secondary outcome measures were designed based on the guidelines for the AYUSH clinical studies in COVID-19 issued by the Ministry of AYUSH. Study design, statistical methods, and data management were also in line with these guidelines.[21]

The severity of COVID-19 was much lesser as assessed by the WHO ordinal scale. Considering that only one subject was positive in the *Chyawanprash* group with mild symptoms as compared with eight subjects who were positive in the control group with symptoms ranging from mild to severe, it may be inferred that the beneficial effects in the *Chyawanprash* group may be attributed to the earlier mentioned various immunological benefits of the formulation, which may help to strengthen the primary defense of the individual for any infection. In addition, the incidences of ILI episodes were also lesser in the *Chyawanprash* group. Although the comparison of the severity of symptoms was not statistically significant between the groups, the number of episodes and subjects with ILI was significantly lesser in the *Chyawanprash* group, which emphasizes the nonspecific immune promotion of *Chyawanprash*. Similarly, the incidence of allergies was also lesser in the *Chyawanprash* group as compared with the control group. This suggests that the regular use of *Chyawanprash* may be helpful in reducing the chances of infection and allergies and also in reducing lesser severity and supporting recovery.

Hence, it may also be seen that the total number of hospitalizations and the average duration of hospital stay were lesser and no ICU admissions were required in the *Chyawanprash* group as compared with the control group. Further, the improvements in a qualitative assessment, such as the QoL, in the *Chyawanprash* group as compared with further deterioration in the control group during the three-month study also show a significant difference between the groups. The global assessment of overall efficacy by subject and physician was very much similar in the *Chyawanprash* group and control group.

In addition, considering the milder and unrelated AEs and SAEs in the *Chyawanprash* group and good patient compliance for *Chyawanprash*, it can be considered as a safe and beneficial preparation as a prophylactic in COVID-19 infection.

Among the key ingredients of *Chyawanprash*, *Amalaki* is well known for its immunomodulatory potential. It is a rich source of vitamin c, minerals, and other vitamins. Pretreatment of experimental animals with *Amla* offered protection against various physical, chemical, and biological stressors and exhibited adaptogenic effects.[22] *Aswagandha* showed a significant immunomodulatory effect in terms of macrophage activity and other parameters, possibly by the induction of lysosomal enzymes and acid phosphatase.[3] *Bhumyamalaki* is traditionally known for its hepatoprotective activity. It was found to have beneficial effects against hepatotoxins such as alcohol[23] and carbon tetrachloride.[24,25]

Chandana (*Santalum album*) has been tested for its antiviral efficacy against the herpes simplex virus[26] through its antioxidant properties. *Draksha* (*Vitis vinifera*) has antioxidant properties. The differential effects of ethanol and grape wine extract on immune functions were studied. Unlike alcohol, grape wine plays a protective role in immune functions despite its alcohol content.[27]

The immunomodulatory effect of Guduchi is established by various experimental studies. In one of the studies, it improved macrophage functions in ochratoxin-A induced mice.[28] *Aswagandha*,[29] *Yashtimadhu*,[30] *Guduchi*,[31] *Pippali*,[32] *and Shalparni*[33] have known antioxidant and immune-boosting properties. The synergistic effects of these various potential ingredients might help to promote immune responses and help reduce the chances of the incidence and severity of the infection.

Although the results of the current study are encouraging, it may also be noted that personal and social hygiene measures, such as the use of handwash, masks, sanitizers, and social distancing, will also be key factors in preventing the chances of COVID-19 infection. In addition, vaccinations as and when available and recommended by the government/health authorities will be necessary in the prevention of infection.

Conclusion

The study concludes that *Chyawanprash* plays a significant role in the prevention of infections, including COVID-19 during the current pandemic. The severity of infection-related illnesses, including COVID-19, was also lower with its consumption. It was found to be safe for consumption in the recommended dose. In view of these data, *Chyawanprash* could be viewed as one of the prophylactic choices in the control of a pandemic such as COVID-19.

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Conflicts of interest

Authors Arun Gupta, Sasibhushan Vedula, Padmanabha Rugvedi, and Rajiva Kumar Rai are currently employed with Dabur India Limited, manufacturers of test product.

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