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Original Research Article

Association between Usage of Prophylactic AYUSH Medicines and Disease Severity in COVID-19 Patients: A Retrospective Cohort Study

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Homeopathy

Abstract

Background Prior vaccination is often studied for its impact on individuals' post-infection prognosis. Ayurveda, Yoga, Unani, Siddha and Homeopathy (AYUSH) medicines, advised by the Government of India as prophylaxis during the first wave of the coronavirus disease 2019 (COVID-19) pandemic, were consumed by the masses in 2020. A study was therefore undertaken to observe any association between the prior usage of AYUSH prophylactic medicines and post-infection severity as reported by recovered COVID-19 individuals.

Methods This was a retrospective, multi-centre, cohort study conducted in 21 cities of India from 5th August to 30th November 2020. Data from recovered COVID-19 patients, of either sex or any age, captured information about AYUSH prophylactic medicines intake prior to infection, disease severity, symptomatology, duration of

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complaints, etc. The study participants were grouped into AYUSH intake and non-intake. Primary composite outcome was the disease clinical course. Secondary clinical outcomes were the rate of and time to clinical recovery.

Results Data of 5,023 persons were analysed. Ayurveda or homeopathic prophylactic medicines were consumed by more than half of the study participants: that is, 56.85% ($n = 1,556$) and 56.81% ($n = 1,555$) respectively. The overall adjusted protective effect (PE) of AYUSH prophylactic intake against moderate/severe forms of COVID-19 disease was 56.7% (95% confidence interval [CI], 48.7 to 63.50; $p < 0.001$). Adjusted PE for homeopathy and Siddha was 52.9% (95% CI, 42.30 to 61.50; $p < 0.001$) and 59.8% (95% CI, 37.80 to 74.10; $p < 0.001$), respectively. A statistically significant association was found between AYUSH prophylactic medicine intake and clinical recovery more frequently by the 3rd day of illness ($\chi^2 = 9.01$; $p = 0.002$). Time to resolution of symptoms in the AYUSH intake group was on average 0.3 days earlier than in the non-intake group ($p = 0.002$).

Conclusion AYUSH prophylactics were associated with statistically significant levels of protection against COVID-19 disease severity. Amongst these, previous intake of homeopathy or Siddha medicines was associated with some protection against moderate/severe illness and with a somewhat quicker clinical recovery. Prospective studies with experimental research design are needed to validate the findings of this study.

Study registration Clinical Trials Registry—India (CTRI/2020/08/027000).

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused considerable morbidity and mortality[1–3] and challenged health care systems worldwide. Diverse preventive and treatment strategies were explored by medical scientists to tackle this previously unknown menace.

Like other countries, India, with the second largest population in the world, faced a huge health care burden due to a scarcity of resources, beds and other necessary infrastructure.[4] In response, the Indian government took rapid measures for control, prevention and management of the disease.[5–7] There were guidelines promoting the use of masks, physical distancing, hand washing, lockdowns, quarantine, epidemiological monitoring, etc., but India also released an advisory promoting the use of 'immunity boosting' AYUSH (Ayurveda, Yoga, Unani, Siddha, Homeopathy) prophylactic medicines.[8–10]

While medical scientists began working on a vaccine for COVID-19, escalating efforts by the Indian government through central and state health advisories and AYUSH immunity campaigns soon led to awareness and utilization of these AYUSH prophylactics by the public at large.[11,12] The use of such 'immune boosters' was also considered to have a beneficial impact on well-being and to be a possible reason for reduced incidence of COVID-19, with lower rates of morbidity and mortality in the country as the number of cases plateaued towards the end of 2020.[13–18]

Vaccines are studied not only for their prophylactic effect on the disease in question but are often also studied for their effect on post-infection prognosis in individuals with prior intake. This stems from the understanding that vaccines may also have a possible role in modulating disease pathogenesis post-infection in cases of failed prevention. Similar studies were conducted even during the early days of the pandemic, where the effects of influenza vaccine on the prognosis of patients testing positive for COVID-19 were explored.[19,20]

The beneficial effect of AYUSH prophylactics in the prevention of COVID-19 has been examined through epidemiological studies in the general population and high-risk groups over time.[21–27] No studies so far, however, have tried to correlate AYUSH prophylactic intake and post-infection disease prognosis.

Our study, through retrospective data collection, aimed to observe any association between the usage of the AYUSH prophylactic medicines (both collectively and individually) and post-infection severity in recovered cases of COVID-19 during the first wave of the pandemic.

Materials and Methods

Study Design and Setting

This was a retrospective, multi-centre, cohort study of recovered COVID-19 patients, conducted in 21 cities of India (Agartala, Bhubaneswar, Bhopal, Chennai, Delhi, Guwahati, Gudivada, Hyderabad, Imphal, Jaipur, Kolkata, Kottayam, Lucknow, Mumbai, Noida, Puri, Puducherry, Ranchi, Siliguri, Surat and Tirupati) during the period from 5th August to 30th November 2020. The wide spread of geographic locations enabled representation from many regions of the country (►**Supplementary file 1**, available in the online version). The study was registered with the Clinical Trials Registry—India (CTRI/2020/08/027000). The study is reported in this paper as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants

The project team at each study site across India collected contact details (address/telephone number) of recovered COVID-19 persons through COVID-19 treatment centres, Central Council for Research in Homeopathy (CCRH) institutes/units, or through private hospitals, as per availability. Wherever necessary, local health authorities were approached to seek access/approval to such individuals.

Study investigators randomly approached potential participants in person or telephonically to assess their eligibility for inclusion in the study, using the following criteria: recovered symptomatic COVID-19 patient (confirmed through RT-PCR or rapid antigen test), of either sex and belonging to any age group, and independently of place of treatment such as home or quarantine centre or hospital. Inclusion was dependent on the receipt of an individual's informed verbal consent to participate.

A recovered patient was considered as an individual who had been discharged from the hospital or who had completed a minimum of 10 days from the date of appearance of first symptoms or testing COVID-19 positive, whichever was the earlier, and who had no fever for 3 days.[28]

Data Collection and Outcome Measures

Data were recorded systematically on pre-designed formats, which captured information related to demography, pre-existing co-morbidities and details of COVID-19 infection. The composite primary outcome of the study was the clinical course of disease, which included disease severity, symptomatology, duration of complaints and requirement for oxygen or ventilator support, and whether they were managed at home or required hospitalization.

Disease Severity

Participants were classified as mild or moderate or severe, as per the Clinical Management Protocol of the Ministry of Health and Family Welfare, Government of India.[29] Disease severity of COVID-19 was also assessed by the World Health Organization (WHO) ordinal scale for clinical improvement.[30]

Mild

Patients with uncomplicated upper respiratory tract infection, having mild symptoms, without evidence of breathlessness or hypoxia (normal saturation), treated with medicines alone at home or at a quarantine/COVID care centre. This category of patients conformed to a WHO ordinal score of 1 or 2 or 3.

Moderate

Patients with signs of pneumonia but no signs of severe pneumonia; presence of clinical features of dyspnoea and/or hypoxia, fever and cough, including SpO_2 <94% (range 90-94%) in room air; treated with medicines + oxygen at home or at a quarantine centre or hospital. This category of patients conformed to a WHO ordinal score of 4.

Severe

Patients with clinical signs of pneumonia (fever + cough + dyspnoea + fast breathing) plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% in room air, treated with medicines + oxygen + ventilator support at home or in hospital. This category of patients conformed to a WHO ordinal score of 5 or 6 or 7.

Secondary clinical outcomes were time to clinical recovery and rate of clinical recovery. Clinical recovery was resolution of three pathognomonic symptoms of COVID-19 (fever + cough + dyspnoea). Time and rate of clearance of these symptoms—alone and in combination—were observed, due to their importance in assessing the need for hospitalization, which in turn has a direct implication on the health care burden and treatment costs.

Obtaining information on quality of life had been envisaged; however, this could not be gathered properly, especially during telephonic interviews. Recording the duration of hospital stay was dropped due to changing governmental policies.

Participants reporting COVID-19 symptoms persisting 1 month beyond the date of appearance of first symptoms were considered to be suffering from post-COVID complaints and were recorded as such.[31]

Further, information about awareness or intake and duration of any AYUSH prophylactic medicines, as per the government advisory[8–10] prior to infection, was also sought (see below). Reported consumption, for any duration and before testing positive for COVID-19, of any prescribed AYUSH prophylactic medicines as per the government advisory was considered as AYUSH intake.

AYUSH Prophylactic Medicines

AYUSH prophylactic medicines, as advocated in the government advisory, included the following[8–10]:

Ayurveda

Samshamani vati, Chyawanprash, Golden milk/haldi, Herbal tea/kadha, giloy, nasal oils, etc.

Yoga

Practice of yoga, pranayama and meditation for at least 30 minutes daily.

Unani

Herbal decoction (kadha) prepared from Behidana (Cydonia oblonga), Unnab (Ziziphus jujube) and Sapistan.

Siddha

Nilavembu kudineer herbal decoction (kadha).

Homeopathy

Arsenicum album 30c, three doses once daily for 3 days; on an empty stomach.

Members of the study team were trained through online discussion/training, to ensure uniformity of study conduct and data collection as per the pre-designed format. Recovered patients were then contacted telephonically/personally, informed about the study objectives and confidentiality of

participants' data and invited to participate in the study after giving verbal consent.

Data collected were recorded into survey forms and then transferred to a spreadsheet. Collated data in the spreadsheet were verified from the forms, anonymized, and then subjected to analysis.

Sample Size

Convenience sampling was adopted, and data of 5,023 recovered COVID-19 patients were gathered over a span of 4 months (5th August–30th November 2020).

Ethics Approval

In view of the prevailing situation of fear amongst the public, transmissibility of the disease, nature of the study and provisions for informed consent for COVID-19 studies by the Government of India,[32] a waiver for written informed consent was granted by CCRH, New Delhi, which approved the study. Verbal informed consent was obtained before enrolling any participant in the study. In the case of children/adolescents below 18 years of age, consent for participation was obtained from the parents. Confidentiality and anonymity of data were maintained throughout the data analysis.

Statistical Analysis

Data captured on survey forms were transferred to a spreadsheet. The categorical data were summarized as frequencies and percentages, whilst quantitative data were reported as mean ± SD.

Awareness and usage of AYUSH prophylactic medicines among the study participants was calculated as percentages. The study participants were classified based on the intake of AYUSH prophylactic medicine as either AYUSH intake or non-AYUSH intake, the latter referred to further here as the non-intake group.

Inter-group comparisons were performed using the chi-square (χ^2) test for categorical data and the independent sample t-test for continuous data. The AYUSH intake and non-intake groups were analysed for clinical outcomes.

We calculated overall odds ratio (OR) for moderate/severe forms of COVID-19, comparing the two groups (AYUSH intake and non-intake) and also in stratified sub-groups, for example, age, sex and co-morbidity. We calculated the protective effect (PE) as 100% × (1–OR) for moderate or severe forms of COVID-19 disease, focusing on the PE of intake of AYUSH medicines overall as well as on PE of intake of each AYUSH modality individually or in combination.

An adjusted OR for moderate/severe forms of COVID-19 disease was calculated using binary logistic regression for AYUSH intake and individual intake of each AYUSH prophylactic, adjusting for age, sex and presence of co-morbidities. Adjusted PE was calculated as 100% × (1–adjusted OR) for moderate or severe forms of COVID-19 disease. OR < 1.0 indicated a protective association.

Kaplan–Meier curve analysis was used to estimate time to clinical recovery or resolution of individual symptoms (fever, dyspnoea and cough) over the first 10 days of illness, and the statistical significance of the difference between the groups was assessed by the log-rank test. Rate of recovery was calculated as a cumulative percentage of participants reporting resolution of the three pathognomonic symptoms in combination or alone.

All results were expressed as mean and 95% confidence interval (CI). A *p*-value less than 0.05 (two-tailed) was considered statistically significant. The analyses were performed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY, United States) and Statcraft version 2. 0 (India).

Results

Demography

Data of 5,023 recovered COVID-19 patients who met the inclusion criteria were subjected to analysis. Out of the study participants, 54.4% ($n = 2,737$) reported intake of AYUSH prophylactic prior to COVID-19 disease, while 45.5% ($n = 2,286$) reported no such intake. The flow diagram of participants is shown in ►**Fig. 1**.

The mean (± SD) age was 42.67 ± 15.01 years in the AYUSH intake group and 41.54 ± 15.41 years in the non-intake group. Participants above 60 years comprised 11.29% ($n = 567$) of the total study participants. The study participants comprised 67.27% ($n = 3,379$) males and 32.73% ($n = 1,644$) females, with 64.59% ($n = 1,768$) males and 35.40% ($n = 969$) females in the AYUSH intake group and 70.47% ($n = 1,611$) males and 29.53% ($n = 675$) females in the non-intake group (►**Table 1**).

Whilst 32.55% ($n = 891$) persons reported a co-morbidity in the AYUSH intake group, 29.13% ($n = 666$) were co-morbid in the non-intake group (►**Table 2**).

Level of Awareness and Usage of AYUSH Preventive Medicines

A majority, 62.61% ($n = 3,145$) of recovered COVID-19 patients, were aware of the Ministry of AYUSH Advisory advocating the use of various AYUSH prophylactic medicines. Amongst the study participants ($n = 2,737$) who reported intake of one or more AYUSH prophylactic medicines before contracting COVID-19 disease, 91.7% ($n = 2,510$) had been aware of the advisory. Of the study participants who did not consume any form of AYUSH medicine ($n = 2,286$) as prophylactic, 27.7% ($n = 635$) had also been aware of the advisory.

AYUSH Intake and Disease Severity

Of the study participants, 69.97% ($n = 1,915$) reported intake of a single AYUSH prophylactic medicine before contracting COVID-19 disease; 28.39% ($n = 777$) reported concomitant intake of two AYUSH prophylactic medicines, while 1.61% ($n = 44$) reported concomitant intake of three AYUSH prophylactic medicines. One person reported intake of all four types of AYUSH prophylactic medicines.

Ayurveda or homeopathic prophylactic medicines were those of choice in the AYUSH intake group, having been consumed by more than half the study participants (i.e., 56.85% [$n = 1,556$] and 56.81% [$n = 1,555$] respectively), followed by 12.02% ($n = 329$) who consumed Siddha medicine

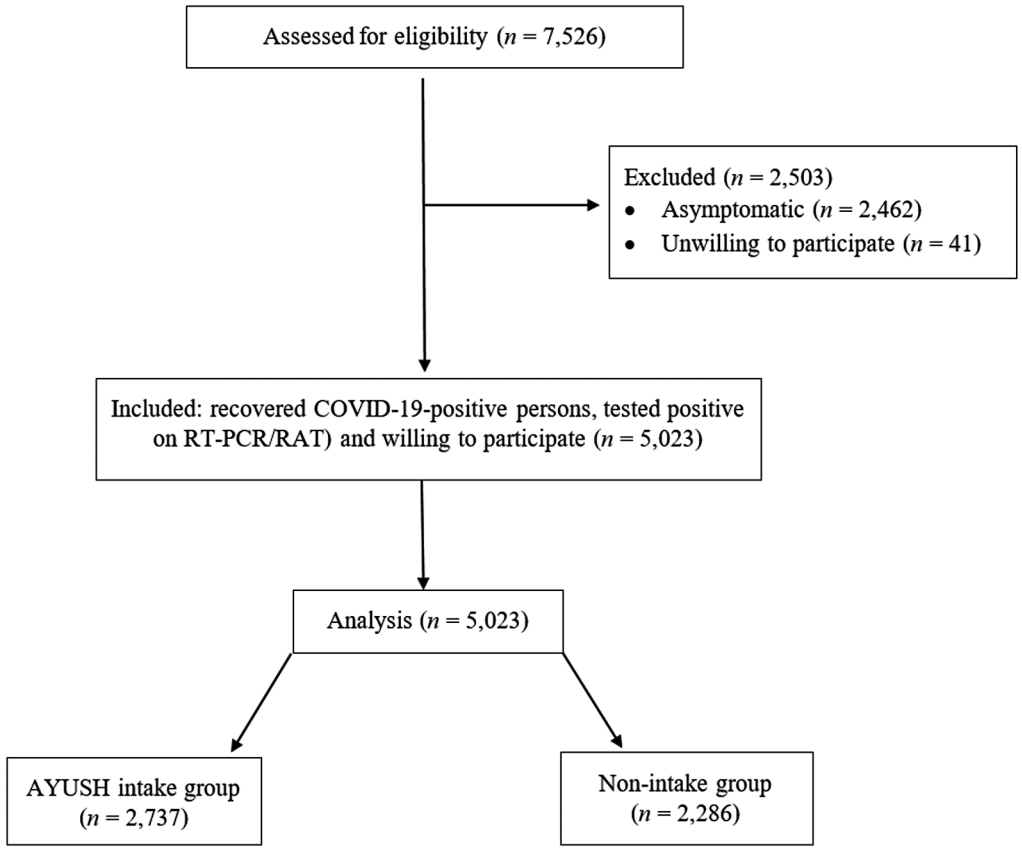

Fig. 1 Participants' recruitment and flow diagram.

and 5.96% [n = 163] who reported doing yoga. Only two participants (0.07%) reported consuming unani medicines. Consumption of homeopathic medicines was reported at all study sites, while Siddha medicines were consumed at one study site only.

It was noted that 89.51% ($n = 2,450$) of individuals who had taken an AYUSH prophylactic were recorded as mildly ill, whereas 81.10% ($n = 1,854$) of the non-intake group reported having had only a mild form of COVID-19.

A significant (and protective) association was found between intake of any AYUSH prophylactic and moderate/severe form of disease (OR, 0.5027; 95% CI, 0.42 to 0.59). The overall unadjusted PE of intake of AYUSH prophylactic medicine against moderate/severe forms of COVID-19 disease was 49.73% (95% CI, 40.94 to 57.20; $p < 0.001$; ►**Table 2**).

Sub-group analysis was done by stratifying the risk factors/confounders such as age group, sex and co-morbidity. There was a significant unadjusted PE of the AYUSH prophylactic medicine against moderate/severe forms of COVID-19 disease in all the age groups (range, 45.79–77.87%). The PE was greatest in the 0 to 20 years age group (i.e., 77.87%; 95% CI, 18.04 to 94.02) and least in the 21 to 40 years age group (i.e., 45.79%; 95% CI, 24.53 to 61.07). Participants aged >60 years, who are at risk of severe outcomes, were significantly protected by the take of AYUSH medicine (PE, 54.75%; 95% CI, 35.15 to 68.42). The PE was 42.79% (95% CI, 30.49 to 52.92) and 61.70% (95% CI, 49.00 to 71.23) in males and females respectively. Details of the outcomes are given in ►**Table 2**.

Binary logistic regression was performed to assess the impact of several factors on the likelihood that the persons would suffer from moderate/severe forms of COVID-19 disease. The model contained four independent variables (use of AYUSH prophylactic medicine, age, sex, co-morbidity). AYUSH intake made a statistically significant contribution to the model. After adjusting the effects of other factors, the adjusted PE of intake of AYUSH prophylactic medicine against moderate/severe forms of COVID-19 disease was 56.7% (95% CI, 48.7 to 63.50; $p < 0.001$) (►**Table 2**).

AYUSH Intake (each AYUSH medicine) and Disease Severity

PE was calculated for participants who consumed different AYUSH prophylactic medicines. Significant unadjusted PE against moderate/severe forms of COVID-19 disease was found for intake of ayurveda, yoga, Siddha and homeopathy prophylactic medicines, as 30.45% (95% CI, 16.93 to 41.77; $p < 0.001$); 39.98% (95% CI, 03.05 to 62.84; $p = 0.036$); 66.23% (95% CI, 48.16 to 78.00; $p < 0.001$) and 56.2% (95% CI, 46.46 to 64.17; $p < 0.001$) respectively. Details of the outcomes are given in ►**Table 2**.

Binary logistic regression was performed to assess the impact of several factors on the likelihood that a person would suffer from a moderate or severe form of COVID-19 disease. This model contained seven independent variables (use of ayurveda, yoga, Siddha and homeopathy as prophylactic medicines; age, sex and co-morbidity). Intake of Siddha

Table 1 Demographic and epidemiological characteristics of the study cohort

Variable	AYUSH intake group ($n = 2,737$) *n* (%)	Non-intake group ($n = 2,286$) *n* (%)	*p*-Value
Age (mean ± SD, years)	42.67 ± 15.01	41.54 ± 15.41	0.009
0–20	186 (6.80)	145 (6.34)	
21–40	1,079 (39.42)	1,041 (45.54)	
41–60	1,157 (42.27)	848 (37.10)	
61 y and above	315 (11.51)	252 (11.02)	
Sex			
Male	1,768 (64.59)	1,611 (70.52)	0.001
Female	969 (35.40)	675 (29.53)	
Occupation			
Employed/self-employed	1,513 (55.28)	1,367 (59.80)	0.001
Household worker/homemaker	599 (21.89)	414 (18.11)	
Student	241 (8.81)	167 (7.31)	
Retired personnel	132 (4.82)	93 (4.06)	
Health care worker/hospital staff	120 (4.38)	102 (4.46)	
Police/armed forces personnel	78 (2.85)	63 (2.76)	
Unemployed	54 (1.97)	80 (3.50)	
Co-morbidity			
Diabetes mellitus	423 (15.45)	302 (13.21)	0.3368
Hypertension	420 (15.35)	295 (12.90)	
Chronic lung disease (asthma/emphysema/COPD)	61 (2.23)	46 (2.01)	
Cardio-vascular diseases	58 (2.12)	38 (1.66)	
Other chronic diseases	255 (9.32)	224 (9.80)	

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.
Note: *n*, total number of participants of the population.
Note: All variables are expressed as *n* (%).

and homeopathy prophylactic medicines each made a statistically significant contribution to the model (►**Table 2**): after adjusting the effects of other factors, the adjusted PE of Siddha intake and homeopathy intake against moderate/severe forms of COVID-19 disease was 59.80% (95% CI, 37.80 to 74.10; $p < 0.001$) and 52.90% (95% CI, 42.30 to 61.50; $p < 0.001$) respectively.

Time to Recovery

A Kaplan–Meier curve was drawn to compare the times taken for recovery (►**Fig. 2**). We observed that in the AYUSH intake group, time to clinical recovery was on average 0.3 days earlier than that in the non-intake group (intake group: 4.56 ± SE 0.05 days, 95% CI: 4.47 to 4.69; non-intake group: 4.86 ± SE 0.06 days, 95% CI: 4.72 to 4.98; $p = 0.002$).

Comparison of time to fever clearance between the two groups showed earlier recovery in the AYUSH intake group by 0.2 days (intake group: 3.79 ± SE 0.05 days, 95% CI: 3.69 to 3.90; non-intake group: 4.02 ± SE 0.06 days, 95% CI: 3.89 to 4.14; $p = 0.042$) (►**Supplementary File 2**, available in the online version).

For cough between the two groups, time to recovery was earlier in the AYUSH intake group by 0.4 days (intake group: 4.99 ± SE 0.08 days, 95% CI: 4.83 to 5.16; non-intake group: 5.42 ± SE 0.09 days, 95% CI: 5.23 to 5.61; $p = 0.001$) (►**Supplementary File 3**, available in the online version).

When compared for dyspnoea, the AYUSH intake group showed earlier recovery by 0.4 days (intake group: 4.71 ± SE 0.13 days, 95% CI: 4.45 to 4.96; non-intake group: 5.16 ± SE 0.14 days; 95% CI: 4.88 to 5.44; $p = 0.020$) (►**Supplementary File 4**, available in the online version).

Rate of Clinical Recovery/Resolution of Pathognomonic Symptoms

As the median day of recovery in the study participants was 4 days, a comparison of the proportion of recovered participants was made between the groups at the 3rd day of illness to enable drawing conclusions for the effect of prophylactic medicine and to eliminate the natural course of disease as the overriding reason for resolution of symptoms.

By day 3, 47.63% ($n = 1,156$) participants had recovered (resolution of three pathognomonic symptoms) in the

Table 2 Association between AYUSH interventions and moderate/severe forms of COVID-19 in the different risk groups and logistic regression—AYUSH prophylactic medicine intake, predicting the likelihood of a protective effect

Variable	AYUSH intake group ($n = 2,737$)		Non-intake group ($n = 2,286$)		Unadjusted odds ratio (95%CI)	Unadjusted protective effect (%)[a] (95% CI)	*p*-Value[b]	Adjusted odds ratio (95%CI)	Adjusted Protective effect (%)[c] (95% CI)	*p*-Value [d]
	Mild *n* (%)	Moderate/ severe *n* (%)	Mild *n* (%)	Moderate/ severe *n* (%)						
Intake of any AYUSH prophylactic	2,450/2,737 (89.51)	287/2,737 (10.49)	1,854/2,286 (81.10)	432/2,286 (18.90)	0.5027 (0.4280–0.5906)	49.73 (40.94–57.20)	<0.001	0.433 (0.365–0.513)	56.7 (48.7–63.5)	0.001
Age (years)										
0–20	183/186 (98.39)	3/186 (1.61)	135/145 (93.10)	10/145 (6.90)	0.2213 (0.0598–0.8196)	77.87 (18.04–94.02)	0.0240	0.561 (0.314–1.004)	43.9 (−0.4–68.6)	0.052
21–40	1,019/1,079 (94.44)	60/1,079 (5.56)	939/1,041 (90.20)	102/1,041 (9.80)	0.5421 (0.3893–0.7547)	45.79 (24.53–61.07)	0.0003	0.258 (0.145–0.458)	74.2 (54.2–85.5)	0.001
41–60	1,009/1,157 (87.21)	148/1,157 (12.79)	632/848 (74.53)	216/848 (25.47)	0.4292 (0.3405–0.5410)	57.08 (45.9–65.95)	<0.001	0.149 (0.082–0.270)	85.1 (73–91.8)	0.001
61 and above	239/315 (75.87)	76/315 (24.13)	148/252 (58.73)	104/252 (41.27)	0.4525 (0.3158–0.6485)	54.75 (35.15–68.42)	<0.001	–	–	–
Sex										
Male	1,570/1,768 (88.80)	198/1,768 (11.20)	1,320/1,611 (81.94)	291/1,611 (18.06)	0.5721 (0.4708–0.6951)	42.79 (30.49–52.92)	<0.001	1.073 (0.897–1.283)	−7.3 (−28.3–10.3)	0.442
Female	880/969 (90.82)	89/969 (9.18)	534/675 (79.11)	141/675 (20.89)	0.3830 (0.2877–0.5100)	61.70 (49.00–71.23)	<0.001	–	–	–
Co-morbidity										
Present	719/891 (80.70)	172/891 (19.30)	427/666 (64.11)	239/666 (35.89)	0.4274 (0.3397–0.5377)	57.26 (46.23–66.03)	<0.001	2.605 (2.182–3.110)	−160.5 (−211–118.2)	0.001
Absent	1,731/1,846 (93.77)	115/1,846 (6.23)	1,427/1,620 (88.09)	193/1,620 (11.91)	0.4912 (0.3859–0.6253)	50.88 (37.47–61.41)	<0.001	–	–	–
Individual AYUSH prophylactics[e]										
Ayurveda	1,339/1,556 (86.05)	217/1,556 (13.95)	1,854/2,286 (81.10)	432/2,286 (18.90)	0.6955 (0.5823–0.8307)	30.45 (16.93–41.77)	0.001	0.902 (0.750–1.085)	9.8 (−8.5–25)	0.273
Yoga	143/163 (87.73)	20/163 (12.27)	1,854/2,286 (81.10)	432/2,286 (18.90)	0.6002 (0.3716–0.9695)	39.98 (03.05–62.84)	0.0369	0.845 (0.513–1.392)	15.5 (−39.2–48.7)	0.508
Siddha	305/329 (92.71)	24/329 (7.29)	1,854/2,286 (81.10)	432/2,286 (18.90)	0.3377 (0.2200–0.5184)	66.23 (48.16–78.00)	<0.001	0.402 (0.259–0.622)	59.8 (37.8–74.1)	0.001
Homeopathy	1,411/1,555 (90.74)	144/1,555 (9.26)	1,854/2,286 (81.10)	432/2,286 (18.90)	0.4380 (0.3583–0.5354)	56.2 (46.46–64.17)	<0.001	0.471 (0.385–0.577)	52.9 42.3–61.5)	0.001

Abbreviations: 95% CI; 95% confidence interval; AYUSH, Ayurveda, Yoga, Unani, Siddha and Homeopathy; OR, odds ratio.
[a]Unadjusted protective effect (%) for moderate/severe, calculated as 1 − (unadjusted OR)×100.
[b]*p*-Value for unadjusted odds.
[c]Adjusted PE (%) for moderate/severe, calculated as (1 − adjusted OR) × 100.
[d]*p*-Value for adjusted odds.
[e]Unani system ($n = 2$) was not considered for analysis.

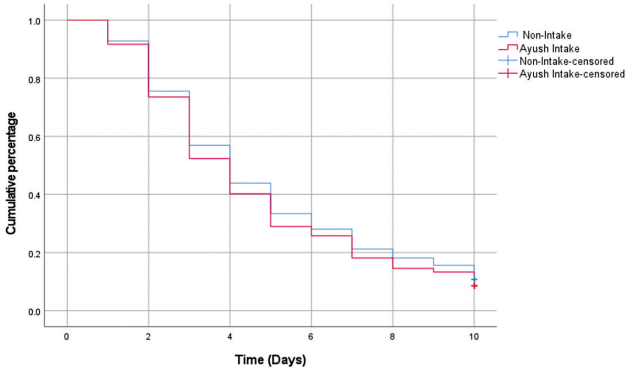

Fig. 2 K–M curve for comparison of time taken for clinical recovery (resolution of pathognomonic symptoms) in AYUSH intake versus non-intake group.

AYUSH intake group in comparison to 43.10% ($n = 849$) in the non-intake group (►**Table 3**). A chi-square test indicated a statistically significant ($\chi^2 = 9.01$; $p = 0.002$) association between intake of AYUSH prophylactic medicine and clinical recovery (resolution of three pathognomonic symptoms) by the 3rd day of illness.

A significant association was found between intake of AYUSH prophylactics and recovery by the 3rd day of disease for the three pathognomonic symptoms individually, that is, fever, cough and dyspnoea respectively ($\chi^2 = 11.95$, $p < 0.005$; $\chi^2 = 14.97$, $p < 0.001$; $\chi^2 = 5.16$, $p = 0.002$).

Stratified analysis showed that previous intake of homeopathic or Siddha prophylactics was significantly associated with clinical recovery more frequently by the 3rd day of illness ($\chi^2 = 6.25$, $p = 0.012$ and $\chi^2 = 25.70$, $p < 0.001$ respectively) (►**Table 3**).

Post-COVID-19 Complaints

1.7% ($n = 72$) out of 4,225 participants who were contacted 1 month after the appearance of first symptoms reported to be suffering from residual/post-COVID complaints. The most frequently reported complaint in this post-COVID-19 group was fatigue, reported by 43.05% ($n = 31$) of this group, followed by cough at 22.22% ($n = 16$).

For participants who took any AYUSH prophylactic medicine ($n = 2,737$), the proportion reporting with post-COVID complaints decreased with the duration of their prior intake of the medicine. Whilst 1.35% ($n = 37$) of participants who had consumed any AYUSH prophylactic medicine in the past for approximately 1 month reported with post-COVID complaints, out of those who had consumed any AYUSH prophylactic medicine for 7 or more months in the past included only 0.15% ($n = 4$) who reported with post-COVID complaints (►**Fig. 3**).

Hospitalization

79.80% ($n = 2,184$) and 74.45% ($n = 1,702$) persons in the AYUSH intake group and non-intake group respectively were treated for their disease at a hospital or a quarantine centre. A total of 13.14% ($n = 287$) in the AYUSH intake group and 25.38% ($n = 432$) in the non-intake group respectively were admitted as above due to their need for oxygen or a ventilator (►**Table 4**). Previous AYUSH intake was significantly associated with reduction in need for oxygen ($\chi^2 = 71.85$; $p = 0.001$).

Discussion

Findings from our study show an association between previous intake of AYUSH prophylactic medicines and better protection against moderate/severe forms of COVID-19 disease. Intake of AYUSH prophylactic medicine had a PE of 56.7% against moderate/severe forms of COVID-19 disease. Out of all the AYUSH modalities, Siddha and homeopathic medicines were significantly associated with protection (59.8% and 52.9% respectively).

Previous intake of Siddha showed a significant PE, though the usage of this AYUSH modality was found to be limited to one study site only and thus is reflective of its positive effect

Table 3 Comparison of clinical recovery at 3rd day of illness/resolution of pathognomonic symptoms between AYUSH intake and non-intake group

	Resolution of pathognomonic symptoms combination by day 3: *n* (%) in the AYUSH intake group	Resolution of pathognomonic symptoms combination beyond day 3: *n* (%) in the AYUSH intake group	Resolution of pathognomonic symptoms combination by day 3: *n* (%) in the non-intake group ($n = 1,970$)	Resolution of pathognomonic symptoms combination beyond day 3: *n* (%) in the non-intake group ($n = 1,970$)	Chi square; *p*-value (intake *versus* non-intake)
AYUSH intake ($n = 2,427$)	1,156 (47.63)	1,271(52.3)	849 (43.10)	1,121 (56.90)	9.0126; 0.0026
Ayurveda ($n = 1,414$)	628 (44.41)	786 (55.58)			0.5801; 0.4462
Homeopathy ($n = 1,367$)	649 (47.47)	718 (52.52)			6.2575; **0.0123**
Siddha ($n = 290$)	171 (58.96)	119 (41.03)			25.7071; **0.001**
Yoga ($n = 148$)	67 (45.27)	81 (54.72)			0.265; 0.6066

Abbreviation: AYUSH, Ayurveda, Yoga, Unani, Siddha and Homeopathy.
Note: Pathognomonic symptoms = fever + cough + dyspnoea.
Note: '*n*' represents the number of participants who presented with this symptom combination.

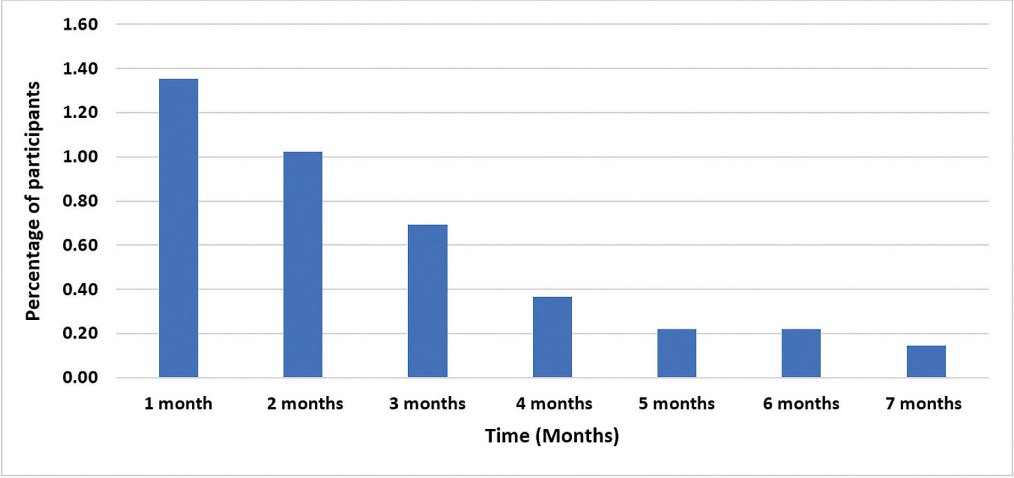

Fig. 3 Participants reporting with post-COVID complaints versus duration of AYUSH intake.

on individuals from one particular Indian state. Usage of homeopathy medicine, however, was reported from all sites from different parts of India, whose populations vary greatly in their cultural, dietary and health behaviours. This establishes that the homeopathy prophylactic had some effectiveness independently of such regional population differences. Similar observations were also made in previous COVID-19 prophylaxis studies of homeopathic medicine.[27,33]

Awareness of the government advisory about AYUSH prophylactics for COVID-19 in more than 60% of the study participants and intake of medicine by 91% of this population reflect on the effectiveness of this governmental strategy in striving to mitigate the pandemic during its first wave.

India has been known to have managed the first wave with a relatively lower fatality rate than most developed countries despite its huge population density, burden of co-morbidities, poor health behaviours and overall disease burden.[32] Though many factors, such as swift government action for a nationwide lockdown, compliance with preventive strategies and the possible role of previous exposure to cross-linked microbes, may have contributed to the low rates of COVID-related fatalities, high usage of AYUSH prophylactics by the masses and its apparently protective impact against disease severity seems to support its positive role.[13–18]

Our study is the first of its kind that explores the association between the consumption of AYUSH prophylactics and disease severity of COVID-19. AYUSH medicines, unlike vaccinations, are not known to produce antibodies against the disease but some have shown some evidence of protection against COVID-19 disease.[21,22,25] In our study, the medicines have shown an evident protective effect against moderate/severe forms of disease, which could be due to as-yet unexplored 'immunity boosting' properties that bring about modulation of disease outcome.

Table 4 System-wise stratified analysis of treatment at health care facility and need for oxygen/ventilator

Treatment facility	Non- intake ($n = 2,286$) *n* (%)	AYUSH intake ($n = 2,737$) *n* (%)	Ayurveda ($n = 1,556$) *n* (%)	Yoga ($n = 163$) *n* (%)	Siddha ($n = 329$) *n* (%)	Homeopathy ($n = 1,555$) *n* (%)
Home	584 (25.55)	553 (20.20)	273 (17.54)	37 (22.70)	32 (9.73)	378 (24.31)
Hospitalized/quarantine centre	1702 (74.45)	2,184 (79.80)	1,283 (82.46)	126 (77.30)	297 (90.27)	1,177 (75.69)
Treated at hospital/ quarantine centre with medicine only	1,270 (74.62)	1,897 (86.86)	1,066 (83.09)	106 (84.13)	273 (91.92)	1,033 (87.77)
Treated at hospital/ quarantine centre with medicine + oxygen	394 (23.15)	272 (12.45)	206 (16.06)	18 (14.29)	24 (8.08)	137 (11.64)
Treated at hospital/ quarantine centre—ventilator	38 (2.23)	15 (0.69)	11 (0.86)	2 (1.59)	0	7 (0.59)

Abbreviation: AYUSH, Ayurveda, Yoga, Unani, Siddha and Homeopathy.
Note: Unani system ($n = 2$) was not considered for analysis.

Every study has its limitations. This study, being retrospective in design, is prone to recall bias on the part of the study participants. This may be true for their reporting duration of intake of AYUSH prophylactics, and time of resolution of symptoms or post-COVID complaints—some of which may have been trivial. By contrast, however, it can be seen that the chances of a person incorrectly reporting about a severe disease or the need for oxygen or ventilatory support are low indeed.

Another potential study limitation is the absence of a concurrent control group, because of which the groups were stratified amongst themselves for comparison of the findings. Information about the lifestyle practices followed by participants, which might have had a role in disease outcome, did not fall within the scope of this study. A prospective study design, capturing information about prophylactic consumption of AYUSH medicines and about contraction of and recovery from infection, might give more robust data.

Conclusion

AYUSH prophylactics were overall associated with statistically significant levels of protection against moderate/severe forms of COVID-19 during the first wave of the pandemic in India. Amongst these medicines, previous intake of homeopathy or Siddha prophylactics was associated with some protection against moderate/severe disease and a clinical recovery more frequently by the 3rd day of illness. Prospective studies with experimental research design are needed to validate the findings of this study.

Highlights

- A retrospective multi-centre study was undertaken in recovered COVID-19 patients to observe any association between usage of AYUSH prophylactic medicines and post-infection severity of COVID-19 during the first wave of the pandemic in India.
- Ayurveda or homeopathy prophylactic medicines were consumed before COVID-19 infection by more than half the study population—that is 56.85% ($n = 1{,}556$) and 56.81% ($n = 1{,}555$) respectively.
- The overall adjusted protective effect of intake of any AYUSH prophylactic medicine against moderate/severe forms of COVID-19 disease was 56.7%.
- Adjusted protective effect of Siddha and homeopathy intake against moderate/severe forms of COVID-19 disease was 59.8% and 52.9% respectively.
- Previous intake of homeopathic prophylactic was significantly associated with clinical recovery (resolution of three pathognomonic symptoms) more frequently by the 3rd day of illness.
- Clinical recovery in the AYUSH intake group was 0.3 days on average earlier compared to the non-intake group.
- Prior intake of AYUSH prophylactics was significantly associated with a reduced need for oxygen or a ventilator.

Supplementary Material

Supplementary File 1. Geographic location of study sites across India.
Supplementary File 2. K-M curve for comparison of time taken for fever clearance in AYUSH intake versus non-intake group.
Supplementary File 3. K-M curve for comparison of time taken for cough resolution in AYUSH Intake versus non-intake group.
Supplementary File 4. K-M curve for comparison of time taken for dyspnea resolution in AYUSH Intake versus non-intake group.

Author Statement

A.C. and D.N. conceptualized the study and developed the protocol and the standard operating procedure (SOP) document. S.P., V.S., M.K., V.P., V.P., B.V., H.R., S.B., N.P., T.P., R.B., V.S., M.D., G.R., U.P., P.P.P., S.P.G., A.R.S., K.C.M., P.P., A.M., A.S., R.K., N.P., A.S., G.D.N., R.K.S., R.S., L.K., S.S., S.P., A.K.S., A.K., N.K., C.R., B.S.J.R.K., V.S.P.K.S., A.D.K. S.S., S.K., P.R., S.G., R.C.S., T.L.S, G.R.C.R., S.P, S.S., G.C. and L.D. participated in finalization of the study protocol and data collection. A.K. monitored the study implementation and provided approvals and inputs for SOP development. A.C. was responsible for overall study administration and coordination with the team at the study site for data collection. A.C., D.N. and S.P. analysed the data. A.C. drafted the first version of the manuscript and made changes with relevant suggestions from all the authors. All the authors approved the version submitted for publication.

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Conflict of Interest

None declared.

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