Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Integrative Medicine 53 (2022) 102131

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.sciencedirect.com/journal/european-journal-of-integrative-medicine

Guduchi Ghanavati (Ayurveda medication) improves the perceived immunity in individuals at risk of SARS-CoV-2: A multicentred, controlled, before-and-after study

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ARTICLE INFO

Keywords:
Ayurveda
COVID-19
Guduchi Ghanavati Immune status
Quality of life
SARS-CoV-2

ABSTRACT

Introduction During the COVID-19 pandemic in India, Ayurvedic medication (*Guduchi Ghanavati,* GG) was prescribed by Ayurveda physicians for prevention and management. This study aimed to evaluate the prophylactic effect of GG in individuals with moderate to very high risk of SARS-CoV-2.

Methods A multicenter, controlled, quasi-experimental, before-and-after study was conducted on individuals at moderate to very high risk of SARS-COV-2 exposure. In the intervention group (n = 15,992), participants received GG 1 g daily for 28 days in conjunction with standard preventive guidelines (SPG), while in the control group (n = 4953), participants were asked to follow SPG only. Outcomes were the incidence of COVID-19, perceived immune status, quality of life, and safety. The perceived immune status was assessed using a brief Likert-scale questionnaire having common immune-related complaints.

Results Of the 20,945 enrolled, 20,574 completed the trial (intervention: 15,729, control: 4845). The percentage of participants who reported the incidence of COVID-19 was marginally lower in the GG+SPG group (41, 0.26%) than in the SPG group (16, 0.33%), leading to 21% (95% CI, -40% to 55%) efficacy of GG. However, the decrease in incidence percentage was statistically insignificant due to the trivial incidences reported. The scores of perceived immune status quality of life improved significantly from baseline in the GG+SPG group ($p < 0.001$) compared to the SPG group.

Conclusion GG is safe and improves perception of immune status in individuals at risk of developing SRAS-CoV-2. However, these findings are inadequate to establish that GG lowers the incidence of COVID-19 necessitating to conduct RCTs in high-risk populations.

Clinical Trial Registration CTRI/2020/06/025,525

1. Introduction

Coronavirus disease 2019 (COVID-19), a global public health emergency, has affected millions of people, causing considerable morbidity and mortality [1]. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted in its new lethal and rapidly transmissible variety, public health concerns have increased [2]. Apart from a few vaccinations, no pharmaceutical drugs have been shown to be effective in the prevention of COVID-19 [3–5]. Even today, the prevention and control of COVID-19 profoundly rely on physical distancing, use of personal protective equipment, and hand cleanliness [6–7].

Ayurveda, a traditional Indian medicine, has the potential to prevent and manage COVID-19. The principles of epidemiology and outbreaks, as well as its containment and management, are well described in Ayurveda, and the principle of increasing the host immune system through Rasayana drugs can be a prophylactic approach [8].

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https://doi.org/10.1016/j.eujim.2022.102131
Received 29 September 2021; Received in revised form 5 April 2022; Accepted 6 April 2022
Available online 28 April 2022

The Ministry of AYUSH (MoA, administrative body of traditional health systems in India) has published a guideline, "National Clinical Management Protocol for COVID-19 Based on Ayurveda and Yoga," which includes Ayurveda measures for the prevention and management of COVID-19 according to the severity of the disease. This guideline was developed based on the Ayurveda classics, clinical experience, empirical evidence, biological plausibility, and emerging patterns from ongoing clinical trials [9]. It is asserted that the reduced death rate due to COVID-19 in India is claimed to be due to the adoption of immunity-promoting medications by people from traditional systems such as Ayurveda. According to the protocol, *Guduchi Ghanavati* (also known as *Samshamani Vati*, prepared from the aqueous extract of *Tinospora cordifolia* Miers) was recommended as a prophylactic drug for high-risk populations of SARS-CoV-2 infection [9].

The literature review revealed that Tinospora cordifolia possesses antimicrobial, anti-oxidant, antitoxic, antidiabetic, hypolipidermic, anti-malarial, anti-neoplastic, hepatoprotective, wound healing and immunomodulatory activities [10–13]. Study investigating the immunomodulatory and anti-SARS-CoV-2 potential of *Guduchi* through network pharmacology and molecular docking, confirmed its role as a prophylaxis in SARS-CoV-2 infection due to its potential to suppress SARS-CoV-2 replication [14,15]. Antiviral activity of *T. cordifolia* against SARS-CoV-2 is by directly inhibiting 3C-like protease (3CLpro), the main protease found in coronaviruses [16]. Guduchi also reversed SARS-CoV-2 viral spike-protein induced disease phenotype in the xenotransplant model of humanized zebrafish [17]. These findings indicate immunomodulatory and anti-SARS-CoV-2 activities of *Guduchi* which needs to be confirmed and established in humans through clinical studies.

In addition, it is critical to understand the influence of such pandemics on mental health and other aspects of life. Psychological effects and immunological responses are linked to the COVID-19 pandemic [18, 19]. Interventions with prophylactic potential against SARS-CoV-2 are required to investigate their influence on general population health and quality of life (QoL). This study aimed to evaluate the prophylactic effect of *Guduchi Ghanavati* (GG) in people with moderate to very high risk of SARS-CoV-2 infection through the incidence of COVID-19, perception of immunity, and QoL.

2. Materials and methods

2.1. Trial design

This trial was a multicenter, prospective, controlled, before-and-after quasi-experimental study. The study was carried out in five cities (Ahmedabad, Vadodara, Bhavnagar, Gandhinagar, and Jamnagar city) in Gujarat state, India.

2.2. Participants

The target population for the trial was people who had a medium to very high risk of exposure to SARS-CoV-2 infection of any sex in the age group of 18 to 68 years, such as health care personnel directly or indirectly involved in COVID-19 management, front-line city/community workers, family members of COVID-19 cases (direct contact), people who inhabit quarantine, containment, and high flow/density population areas. Participants who were less exposed to SARS-CoV-2 or confirmed cases of COVID-19; pregnant and lactating females, known cases of uncontrolled diabetes, and hypertension or any other systemic uncontrolled conditions; an immune-compromised condition, such as HIV, hepatitis, tuberculosis, or cancer; any medical or surgical condition requiring immediate medical or surgical intervention; and those receiving any type of immunosuppressive therapy were excluded at the time of screening. A four-point ordinal scale (lower, medium, high, and very high) was developed that measures the risk of exposure according to the Occupational Safety and Health Administration's risk classification guidelines for occupational exposure to SARS-CoV-2 [20], the details of which are mentioned in the Supplemental File S1.

Individuals from the target population were recruited from the community-based public settings of five cities in Gujarat state, India, from June 9, 2020, to October 22, 2020. Initially, the team received a list of some individuals at high risk from the local health administration employee roster, and the recruitment process was initiated. To escalate recruitment further, the research team under local health administration guidance spotted high-risk areas and identified potential individuals such as quarantine personnel, dweller of COVID-19 hotspot zones, and close contact with COVID-19 patients. Thus, a small fraction of the screened potential individuals at high risk to SARS-CoV-2 were received from the government, and the research team themselves listed remaining out. All accessible individuals of high-risk areas were contacted door-to-door at their homes or places of employment and interviewed face-to-face for eligibility.

Individuals who met the criteria were invited to participate in the study and informed consent was obtained. Those who opted to participate were further examined to determine the baseline status of the outcome variables. Participants were assigned to a trial arm based on their choices. Participants who chose to take GG were assigned to the intervention group and received an entire course of trial drug with instructions, while those who opted out of receiving prophylaxis medicine were recruited as controls. Both groups were instructed to follow standard preventive guidelines (SPG). Patient's adherence to the protocol was recorded through the patient diary. Patients were instructed to complete a diary on a daily basis for dose and time of medication. At fortnightly intervals, all participants were contacted by telephone to assess adherence. The adherence percentage (number of pills taken during a specific period divided by the number of pills prescribed during the same period) was then computed using the patient diary and transformed to an ordinal scale [poor (50%), moderate (50 to 80%), and good (>80%). At the end of the trial, the outcome data were obtained by telephone contact with the registered participants.

Study team members were trained in community-based recruitment strategies and activities before commencing the trial. The study was prospective in which baseline data on individuals were obtained first, followed by intervention and follow-up over time to evaluate the effects on the intended outcome.

2.3. Sample size

The effect size of the trial drug could not be estimated for the primary outcome, as this was the first study of its kind. Considering that it was a population-based trial, the sample size was fixed at 20,000 participants. Due to the high demand for Ayurveda medicines in the Indian population during the pandemic, a 3:1 enrollment ratio was assumed for the intervention to control.

2.4. Intervention and control

The study drug "*Guduchi Ghanavati*" was obtained from the Indian Medicines Pharmaceutical Corporation Limited (IMPCL) Almora, Uttarakhand, India. Each tablet consisted of 250 mg of dry concentrated aqueous extract of the stem of *Guduchi* (*Tinospora cordifolia)*. The trial drug was administered in a dose of two tablets (total 500 mg) twice daily, that is, 1 g/day orally after food for 28 days from baseline, and participants were instructed to follow the standard SARS-CoV-2 infection prevention guidelines (frequent hand washing, physical distancing, and covering the mouth and nose). The control group was advised to adhere to SPG only. This was performed for a duration of 28 days.

2.5. Primary outcome

2.5.1. Incidence of COVID-19

The primary outcome was the incidence of SARS-CoV-2 infection

(COVID-19 test-positive) in participants through self-reporting. The diagnostic policy for COVID-19 in Indian governments prevalent at that time is provided in Supplementary File S1. Considering the lack of reverse transcription–polymerase chain reaction (RT-PCR) test availability and administrative policy, the rapid antigen test was also used to confirm the diagnosis of COVID-19.

2.6. Secondary outcomes

2.6.1. Immune status (ISQ score) [21]

The status of the perception of immune was determined using the immune status questionnaire (ISQ). The ISQ consists of seven items (common cold, diarrhea, sudden high fever, headache, muscle and joint pain, skin problems, and coughing). The items were classified on a 5-level Likert scale ranging from) to 4 (0, never; 1, sometimes; 2, regularly; 3, often; 4, almost [always]), stating how often the participants experienced these complaints. The converted ISQ score ranged from 0 to 10, and higher scores corresponding to better immune functioning were used for the analysis. A single item question ranging from 0 (very poor) to 10 (excellent) was used for perceived immune functioning and perceived overall health status.

2.6.2. WHOQOL-BREF [22]

QoL was measured using the World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF) at baseline and the end of the trial. It consists of 24 items (Likert scale score) to assess the perception of the QoL in four domains: physical health, psychological, social relationships, and environment. Individual domain scores were converted to a linear scale between 0 and 100, with a higher score indicating better QoL.

Safety:

The incidences adverse events encountered during the clinical study were recorded on Case Record Form. Severity of events were graded on a three-point scale (mild, moderate, severe) and its relationship to treatment was categorised in six categories (certain, probable, possible, unlikely, unclassified, unassessable) and assessed [23].

2.7. Statistical methods

Data were analyzed using IBM SPSS version 27. The primary outcome was analyzed using the risk ratio (RR), odds ratio (OR), adjusted odds ratio, and relative risk reduction (efficacy%). Continuous variables were evaluated using the paired *t*-test and analysis of covariance (ANCOVA) test for within-group and between-group analyses. Nonparametric tests, such as the Wilcoxon signed-rank test and the Mann−Whitney U test, were used to evaluate ordinal data for comparisons within and between groups. The effect size on secondary outcomes was represented by Cohen's *d*. Through bivariate logistic regression, the primary outcome was adjusted for age, sex, education, risk of exposure to SARS-Cov-2, and morbidity. Additionally, a subgroup analysis was performed for age category, exposure level, morbidity status, sex, economic status, religion, habitat and marital status. Correlations between perceived immune status and QoL were analyzed using Pearson's product moment coefficient (r). The confidence level was set at 95%, and p-values of less than 0.05 were considered significant.

2.8. Ethical approval and registration

The study was approved by the Institutional Ethics Committee, IPGT&RA, Jamnagar (approval no. PGT/7/-A/Ethics/2020–21/239 dated May 28, 2020), registered in the Clinical Trial Registry of India (CTRI/2020/06/025,525), and conducted according to the guideline of the Indian Council for Medical Research of good clinical practice.

3. Results

From June 9 to October 22, 2020, among 21,888 participants screened, 943 were found not to satisfy eligibility criteria and therefore, were excluded. Further, as 452 participants declined to participate, remaining 20,945 were included. Of these, 15,992 participants received GG with SPG (GG+SPG), whereas 4953 participants received SPG only. In the GG+SPG group, 89 participants dropped out, 18 terminated due to adverse events, and 156 were lost to follow-up; in the SPG group, 108 patients dropped out. Data from the remaining participants (GG+SPG, 15,729; SPG, 4845) were analyzed for the outcomes (Fig. 1). Recruitment was stopped once a predefined sample size was reached.

The baseline characteristics obtained from the participants in both groups are shown in Table 1. The mean age of the participants was 38.7 ± 12.1 years and 37.2 ± 12.4 years in the GG+SPG and SPG groups, respectively. The male: female ratio was 2.6:1 in the GG+SPG group and 1.88:1 in the SPG group. In the GG+SPG group, 58.7%, 31.3%, and 10% of the participants had a medium, high, and very high risk of exposure to COVID-19, respectively. Meanwhile, in the control group, 74%, 23.1%, and 2.9% participants had medium, high, and very high risk exposure to COVID-19, respectively. A total of 6.4% of the participants reported morbidity in the interventional group and 3.8% in the control group. A total of 9878 (48%) participants were recruited from the study site in Ahmedabad, 4878 (23.7%) from Vadodara, 2709 (13.2) from Gandhinagar, 1497 (7.3%) from Bhavnagar, and 1612 (7.8%) from Jamnagar (Table 1). At baseline, demographic characteristics was uniformly distributed between groups.

3.1. Incidence of COVID-19

COVID-19 incidence was reported by 41 (0.26%) participants in the GG+SPG group and 16 (0.33%) participants in the SPG group. Although the incidence was higher in the control group, the difference was not statistically significant between the two groups (RR and OR, 0.79; 95% CI, 0.44−1.40; adjusted OR, 0.67; 95% CI 0.37−1.21). The efficacy (relative risk reduction) of GG was 21% (95% CI, −40% to 55%) higher than that of SPG, but the difference was not statistically significant (Table 2).

3.2. Changes in immunity

Data on the perceived immune status of participants are presented in Table 3. The mean score of ISQ increased significantly ($p < 0.001$) from baseline to EOT in both groups. The perceived immune function score of 1 item was significantly ($p < 0.001$) improved in the GG+SPG interventional group only. Perceived general health also improved in both arms ($p < 0.001$ in GG+SPG, $p = 0.04$ in SPG). Compared to SPG, GG+SPG significantly improved the mean score of immune score, immune function, and general health ($p < 0.001$). The effect size (Cohen's *d*) of GG+SPG compared to SPG was small [ISQ (*d*): −0.24, immune function; (*d*): −0.13, general health].

3.3. Changes in quality of life

Table 4 shows the WHOQOL-BREF score for each QoL domain for participants in the GG+SPG and SPG groups. Both groups had similar scores across all four domains at baseline (for the GG+SPG and SPG groups, respectively, 76.14 vs. 77.02 in the physical domain, 71.77 vs.71.52 for the psychological domain, 64.47 vs. 65.25 in the social relationships domain, and 70.05 vs. 70.71 in the environmental domain).

Among the participants in the GG+SPG group, QoL scores improved significantly ($p < 0.001$) in all four domains of their baseline scores, whereas in the SPG group, mean scores increased in two domains, psychological ($p < 0.001$) and environmental ($p = 0.007$). At the end of the trial, the mean score improvement from baseline was considerably

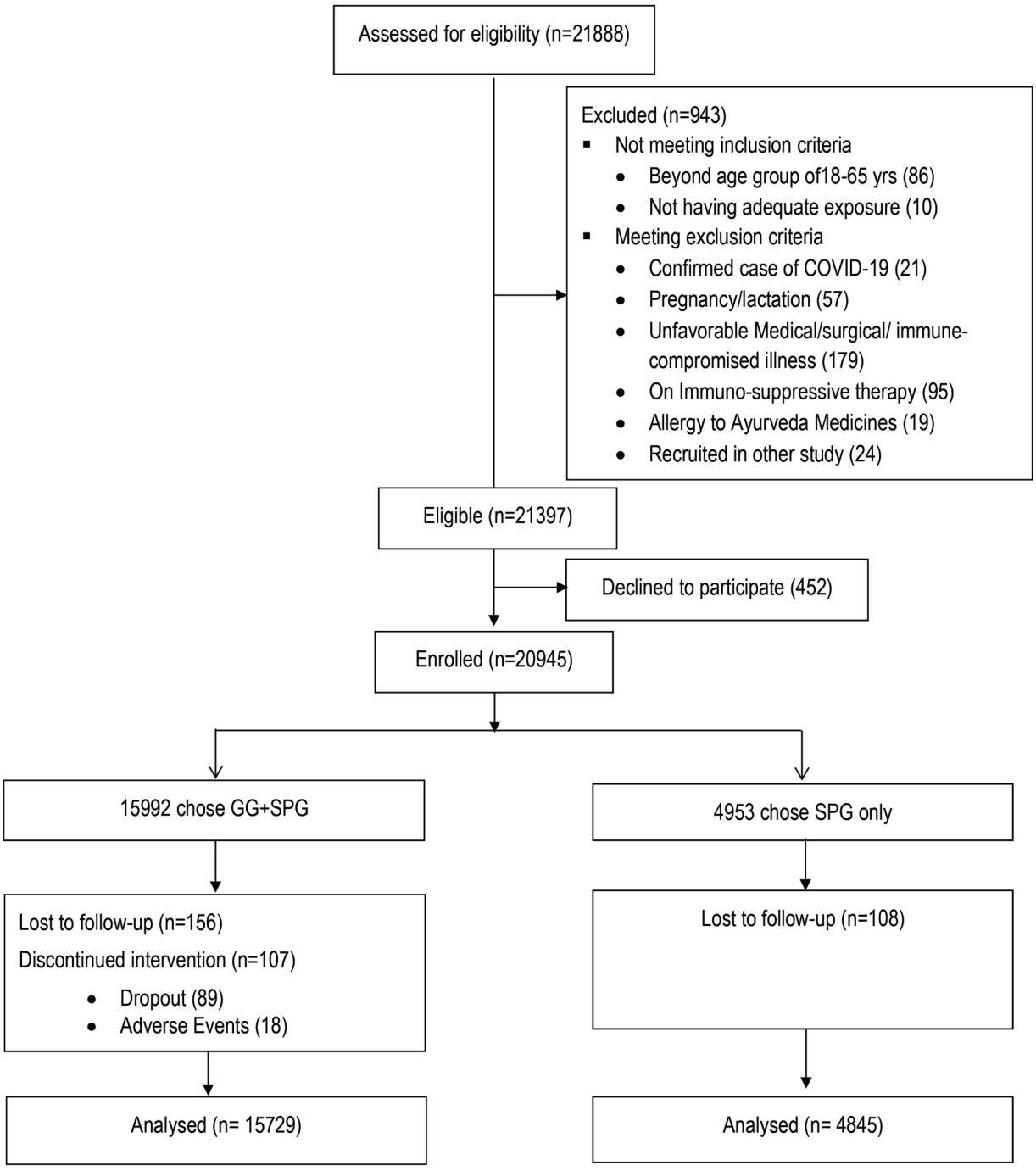

Fig. 1. Flow diagram for the Guduchi Ghanavati before-and-after control study.

higher in the GG+SPG group than in the SPG group for all four domains [physical: $\bar{x}$ (SD)=2.48 (13.68), psychological: $\bar{x}$ (SD)=1.6 (13.97), social relationships: $\bar{x}$ (SD)=1.78 (18.73), and environmental: $\bar{x}$ (SD)=2.12 (14.53)]. The effect size (Cohen's *d*) of GG+SPG compared to SPG was small for all domains [physical (*d*): −0.24; psychological (*d*): −0.22; social relationships (*d*) −0.14; and environmental (*d*): −0.24]

3.4. Correlation between perceived immunity and QoL

Table 5 illustrates the baseline correlations between perceived immune status, general health, and QoL. There was a positive correlation between perceived immune status and all domains of QoL. Immune status was strongly associated with general health (r = 0.826) and weakly associated with QoL. Moderate to strong associations were observed among all QoL domains. The physical, psychological, and environmental domains were strongly associated with each other. The social domain was also moderately associated with other QoL domains.

3.5. Adverse events reported

No serious adverse events were reported among the participants of the test drug group. In the GG+SPG group, of 18 non-serious adverse events reported, 17 events were mild and only 1 event had moderate severity. These events included gastric discomfort, diarrhea, and headache, common cold, throat pain, stomatitis, cough, weight gain, piles, weakness, and fever. Causality assessment showed that 'gastric

Table 1
Demographic characteristics of the participants (n = 20,574).

Variables	Category	GG+SPG (n = 15,729)	SPG (n = 4845)
Age (Mean, SD)	–	38.7 (12.1)	37.2 (12.4)
Age (categorical), n (%)	18–33	6822 (43.4%)	2368 (48.9%)
	34–51	5467 (34.8%)	1598 (33%)
	52–68	3440 (21.8%)	879 (18.1%)
Sex, n (%)	Male	11,393 (72.4%)	3164 (65.3%)
	Female	4336 (27.6%)	1681 (34.7%)
Education, n (%)	Illiterate	2707(17.2%)	652 (13.5%)
	Able to read & write	13,022 (82.8%)	4193 (86.5%)
Occupation, n (%)	Desk work	8693 (55.3%)	2958 (61.1%)
	Physical	1766 (11.2%)	238 (4.9%)
	Field work	4427 (28.1%)	1201 (24.8%)
	housewife	843 (5.4%)	448 (9.2%)
socioeconomic status, n (%)	above poverty line (apl)	15,408 (98%)	4689 (96.8%)
	Below poverty line (BPL)	321 (2%)	156 (3.2%)
Habitat, n (%)	Urban	15,617 (99.3%)	4738 (97.8%)
	Semi-urban	85 (0.5%)	102 (2.1%)
	Rural	27 (0.2%)	5 (0.1%)
Marital status, n (%)	Married	12,880 (81.9%)	3844 (79.3%)
	Unmarried	2748 (17.5%)	953 (19.7%)
	Widow	79 (0.5%)	42 (0.9%)
	Divorcee	22 (0.1%)	6 (0.1%)
Religion, n (%)	Hindu	15,140 (96.3%)	4687 (96.7%)
	Muslim	568 (3.6%)	154 (3.2%)
	Sikh	3 (0.0%)	2 (0.0%)
	Christian	18 (0.1%)	2 (0.0%)
Exposure risk to COVID-19, n (%)	Medium	9236 (58.7%)	3584 (74%)
	High	4926 (31.3%)	1119 (23.1%)
	Very High	1567 (10%)	142 (2.9%)
Comorbidity presence	Yes	1012 (6.4%)	184 (3.8%)
	No	14,717 (93.6%)	4661 (96.2%)
Study sites	Ahmedabad	7923 (50.4%)	1955 (40.3%)
	Vadodara	3542 (22.5%)	1336 (27.6%)
	Gandhinagar	1986 (12.6%)	723 (14.9%)
	Bhavnagar	1120(7.1%)	377 (7.8%)
	Jamnagar	1158 (7.3%)	454 (9.4%)

GG, *Guduchi Ghanavati*; SPG, standard preventive guidelines; SD, standard deviation

Table 2
Incidence of COVID-19 cases among groups and its risk estimates.

Group	**COVID-19 positive**	
	Yes	No
GG+SPG	41 (0.26%)	15,688 (99.74%)
SPG	16 (0.33%)	4829 (99.67%)
Effect Estimate and efficacy (%)		
Effect Estimate	**Value**	**95% CI**
Relative Risk	0.79	[0.44 to 1.41]
Odds Ratio	0.79	[0.44 to 1.41]
Adjusted Odds Ratio	0.67	[0.37 to 1.21]
Efficacy (%)	21%	[−40% to 55%]

CI, confidence interval.
[a]adjusted for age, sex, economic status, education level, risk level of exposure to SARS-CoV-2, and presence of morbidity.

discomfort' was drug-related adverse event, whereas diarrhea may have possibly relation to test drug. Other events were unlikely related to GG. However, the proportion of participants who reported adverse events was negligible (Table 6).

3.6. Drug adherence

Among all participants, 89.7% had good adherence to the trial drugs, followed by moderate adherence (6.7%). The incidence of COVID-19 was lower in moderate-to-good adherence to the trial drug than in poor adherence, implying that adherence to GG is related to a lower incidence of COVID-19. However, it needs further confirmation, as the frequency of the outcome is less (Table 7).

3.7. Subgroup analysis

Subgroup analyses were performed for the primary outcome on binary variables of age (age, ≤50 and >50), exposure level (medium, high to very high), status of morbidity (present or absent), sex (male, female), economic status (APL, BPL), religion (Hindu, Muslim), habitat (urban, other) and marital status (married, unmarried). The efficacy of GG+SPG compared to SPG did not change remarkably for variables such as age, morbidity, sex, economic status, religion, habitat and marital status in the subgroup analysis. However, when participants were stratified according to their risk of exposure, the efficacy was considerably altered, as the incidence of COVID-19 was significantly lower in GG+SPG than in SPG in participants with high to very high risk. In the high-risk subgroup, the efficacy of GG+SPG was 59% (CI 16% to 80%) greater than that of SPG. Due to the small number of incidents, these findings should be considered with caution (Table 2 in Supplementary File S1). Similarities in outcome measures among sub-groups validates the study finding and ensures the generalizability among Indian population having diverse characteristics.

4. Discussion

To the best of our knowledge, this is the first study of its kind that has evaluated the prophylactic effect of GG in people with moderate to high risk exposure to COVID-19 by reporting the incidence of COVID-19, perceived immunity, and QoL. This study showed that oral administration of 1 g of GG daily for 28 days marginally reduced the incidence of COVID-19 compared to those who did not receive the prophylaxis drug. This statistically insignificant reduction can be attributed to a trivial occurrence reported by the participants, which can be further explained by the reduction in cases of COVID-19 at the study sites during the study period and the registration of the moderate risk group. In the subgroup analysis, the incidence of COVID-19 was significantly lower in the GG+SPG group than in the SPG group among high-risk subjects.

Guduchi is an essential "Rasayana" [24] drug that exhibits anti-depressive, anxiolytic [25,26], and immune-modulatory effects [12] through stimulation of nonspecific immune mechanisms [27]. Borse et al. established the mechanism by which GG modulates several immune pathways through bioactive target associations and showed that GG has the potential to inhibit the replication of SARS-CoV-2 using network pharmacology and in silico approaches [14,15]. Such properties of *Guduchi,* which modulate several immune pathways, are likely to explain the significant improvement in perceived immunity status and QoL reported in the present study. Improved QoL following SPG alone may be associated with increased awareness and education about the new pandemic situation.

For clinical significance, efficacy (%) (relative risk reduction) for the primary outcome and Cohen's d effect size for other outcomes were calculated. Furthermore, the relatively small effect size (Cohen's d) of the intervention on secondary outcomes might be due to the relatively shorter duration of the trial or the comparatively healthy status of most participants since baseline. In an earlier study in GG, the therapeutic

Table 3
Analysis of the immunity status parameters within and between the groups.

Immune status	GG+SPG, mean (SD)				SPG, mean (SD)				comparison between groups		
	Baseline	EOT	Change	sig. P[a]	Baseline	EOT	Change	sig. P[a]	Mean difference (SD)	sig. (p)[b]	*d*
Immune score (ISQ)	9.3 (0.95)	9.6 (0.73)	0.3 (0.9)	<0.001	9.14 (0.93)	9.26 (0.82)	0.11 (0.99)	<0.001	0.28 (0.92)	<0.001	−0.24 (−0.27 to −0.2)
Immune function	8.54 (1.0)	8.69 (1.09)	0.15 (1.09)	<0.001	8.41 (1.03)	8.43 (0.1)	0.02 (0.87)	0.19	0.12 (1.04)	<0.001	−0.13 (−0.16 to −0.1)
General health	8.55 (0.98)	8.66 (1.05)	0.11 (1.06)	<0.001	8.4 (1.02)	8.38 (0.1)	−0.02 (0.89)	0.04	0.08 (1.02)	<0.001	−0.13 (−0.16 to −0.1)

EOT, end of the treatment; *d*, Cohen's *d*; CI, confidence interval.
[a] Wilcoxon signed-rank test for within-group comparison.
[b] Mann−Whitney test for between-group comparison.

Table 4
Comparison of WHOQOL-BREF scores (transformed to 0 − 100 scales) for four domains within and between groups.

WHOQOL-BREF domain	GG+SPG, (mean (SD))				SPG, mean (SD)				comparison between group		
	Baseline	EOT	Change	sig. P[a]	Baseline	EOT	Change	sig. P[a]	Diff in mean change	sig. (p)[b]	*d* (95% CI)
Physical	76.14 (14.87)	79.39 (14.15)	3.25 (14.01)	<0.001	77.02 (13.76)	77 (15.11)	−0.02 (12.2)	0.913	2.48 (13.68)	<0.001	−0.24 (−0.27 to −0.21)
Psycho	71.77 (13.78)	74.12 (13.16)	2.35 (13.96)	<0.001	71.52 (12.6)	70.75 (13.58)	0.78 (13.72)	<0.001	1.6 (13.97)	<0.001	−0.22 (−0.25 to −0.2)
Social	64.47 (18.86)	66.86 (19.48)	2.39 (19.14)	<0.001	65.27 (18.92)	65.06 (18.91)	−0.21 (17.17)	0.393	1.78 (18.73)	<0.001	−0.14 (−0.17 to −0.1)
Environ	70.05 (15.31)	72.99 (14.45)	2.94 (14.5)	<0.001	70.71 (13.81)	70.15 (14.94)	−0.56 (14.31)	0.007	2.12 (14.53)	<0.001	−0.24 (−0.27 to −0.21)

Physical, physical health domain; Psycho, psychological health domain, Social, social relationships domain; Environ, environmental health domain of Quality of Life (WHOQOL-BREF); EOT, end of treatment.; *d*, Cohen's *d*; CI, confidence interval.
[a] paired *t*-test.
[b] ANCOVA test (covariate: baseline).

Table 5
Correlation between perceived immunity parameters and quality of life at baseline.

Parameters	Immune Status	General health	QoL (Physical)	QoL (Psychological)	QoL (Social relationships)	QoL (Environmental)
Immune Status	1	0.83*	0.10*	0.25*	0.03*	0.14*
General health	0.83*	1	0.10*	0.24*	0.02*	0.13*
QoL (Physical)	0.10*	0.10*	1	0.64*	0.55*	0.75*
QoL (Psychological)	0.25*	0.24*	0.64*	1	0.45*	0.74*
QoL (Social relationships)	0.03*	0.02*	0.55*	0.45*	1	0.58*
QoL (Environmental)	0.14*	0.13*	0.75*	0.74*	0.58*	1

Value: Correlation coefficient (r); QoL, quality of life.
*The correlation is significant at the 0.01 level (two-tailed).

benefit in patients with mild COVID-19 was evident by reducing the duration of hospital stay and averting disease progression [28]. No serious adverse events were reported during the study. It was generally well tolerated, and only very few nonserious adverse events were reported, primarily with gastrointestinal symptoms, indicating the relative safety of the drug.

Furthermore, the cost of herb-based drugs is very low (2 USD or 150 INR) compared to certain expensive conventional drugs. In India, GG may be considered a cost-saving drug compared to conventional care, as per-day hospitalization costs range from 77 to 136 USD (5000−10,000 INR). However, a detailed study on the cost-benefit analysis of the drug through an economic model considering diverse outcomes and other related factors is needed.

4.1. Study limitations

This study had several limitations. We were unable to randomly assign participants to arms due to the short duration of the study; therefore, some unavoidable baseline imbalances were observed. To minimize the impact of imbalances, the primary outcome was adjusted for important prognostic factors/confounders. Furthermore, due to the subjective nature of secondary outcomes and unmasked participants, the risk of measurement bias was inevitable. However, it was minimized using validated tools, trained-team for data collection, and monitoring. The incidence of COVID-19 was self-reported by the participants, and asymptomatic cases that were not tested or reported were likely missed. The sensitivity of rapid antigen testing is comparatively low in illness, leading to a lower detection of incidence. The cohort largely comprised

Table 6
Reported adverse events in the GG+SPG group.

Adverse event,	GG+SPG	
	Number of event (n)	Type of event (n)
Any adverse event		
Mild	17	Gastric discomfort (5), Diarrhea (5), Headache (3), Weight increase (2), Weakness (1), Fever (1)
Moderate	1	Piles (1)
Severe	0	–
Causality		
Certain	0	–
Probable/ likely	5	Gastric discomfort (5)
Possible	5	Diarrhea (5)
Unlikely	8	Headache (3), Weight increase (2), Weakness (1), Fever (1), Piles (1)
Unclassified	0	–
Un-assessable	0	–

Table 7
Association between drug adherence level of *Guduchi Ghanavati* and COVID-19 incidence.

COVID POSITIVE	Drug adherence			P
	Poor (1.4%)	Moderate (6.7%)	Good (89.7%)	
No	211 (98.6%)	1054 (99.8%)	14,080 (99.8%)	0.003[a]
yes	3 (1.4%)	2 (0.2%)	33 (0.2%)	

[a] chi square test.

relatively healthy young and middle-aged populations; therefore, further studies are warranted to extrapolate the findings to other populations. It is also limited to the geographical and cultural groups of the study site.

5. Conclusion

Evidence gathered from a multicenter, controlled, before-after trial suggests that GG increases the perception of immune status and QoL; hence, it may be used to improve general health in individuals at high risk of SARS-CoV-2. The data findings are inadequate to show that GG reduces the incidence of COVID-19 in people with moderate to high risk exposure to SARS-CoV-2 due to the reported trivial incidence. Therefore, RCT is recommended in populations at high risk of SARS-CoV-2 for a longer duration to confirm the trends observed in this study.

Financial support

This work was supported by Institute of Teaching and Research in Ayurveda, Jamnagar, Gujarat, India, 361,008 (Grant order no. PGT/COVID19/Research/15)

Ethical approval

The study protocol was approved by the Institutional Ethics Committee, Institute for Post Graduate Teaching and Research in Ayurveda (Approval no. PGT/7/-A/Ethics/2020–21/239).

Data availability

Data linked to this study is available in supplementary file S1.

Extended data associated to this study is available at Zenodo: Clinical Dataset of project 'prophylaxis effect of Ayurveda intervention 'Guduchi Ghanavati' on COVID-19' https://doi.org/10.5281/zenodo.4584445

CRediT authorship contribution statement

Anup Thakar: Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing. **Kalpesh Panara:** Conceptualization, Investigation, Methodology, Project administration, Software, Writing – original draft. **Harshit Shah:** Funding acquisition, Resources, Supervision. **Bharat Kalsariya:** Funding acquisition, Resources, Supervision. **Sweety Ruparel:** Funding acquisition, Resources, Supervision. **Naresh Jain:** Funding acquisition, Resources, Supervision. **Parthiv Bhatt:** Investigation, Writing – original draft. **Dilip Jani:** Investigation, Writing – original draft. **Rajendrasinh Dodia:** Investigation, Writing – original draft. **Falgun Patel:** Investigation, Writing – original draft. **Rohini Salve:** Investigation, Writing – original draft. **Swapnil Chaudhari:** Project administration, Resources, Investigation. **Hemang Raghavani:** Data curation, Formal analysis, Software. **Jatin Vyas:** Investigation, Writing – original draft. **Mandip Goyal:** Methodology, Writing – review & editing. **Sagar Bhinde:** Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest. Testing drug (GG) was procured from Government of India owned pharmaceutical company 'Indian Medicines Pharmaceutical Corporation Limited (IMPCL)' and investigators did not receive any funds or commercial benefits from pharmaceutical company in this trial.

Acknowledgments

We acknowledge Dr. Kalpana Joshi for reviewing the manuscript before submission, Project management unit, Ministry of AYUSH for guidance in development of protocol. We also acknowledge the team members from all sites for their assistance in data collection. They were Harsh Upadhyay, Avani Patel, Nikita Pamnani, Kinjal Unadkat, Alpesh Patel, Ditiksha Chaudhari, Bhavin Chavda, Tejan Bhatt, Hiral Khunt, Nidhi Patel, Jigar Patel, Twinkal Rathod, Hasti Ninama (Baroda center), Zala Hetal, Piprani Nagma, Chauhan Mittal, Dharmendra Darbar, Vishalkumar Parmar, Vipul Parmar (Gandhingar center), Rajdip Rao, Manoj Timbadiya, Devang patel, Smit Thakar (Bhavnagar center), Pratik Mungara, Jaynika Garasia, Dipali Parekh, Seema Kathavadiya, Jalpa Rupareliya, Dinesh Dumadiya, Bhadresh Patel (Jamnagar center), Nirlep Sojitra, Khushbu Prajapati, Harshal Patel, Urvashi Patel, Priya Mehta, Jigna Mahida, Kalyani Ajmera, Pooja Sharma, Dolly Solanki, Rizvan Saiyed, Tejal Ganvit, Swati Thakar, Anjanaben Dabhi, Sonalkumari Patel, Ruksar Piparvadiya, Shivani Patel, Aartiben Aghera, Janki Gajjar, Poonam Bhatti, Neky Mehta, Manmohan Gupta (Ahmedabad center). We would also like to thank Editage (www.editage.com) for English language editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2022.102131.

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