ORIGINAL RESEARCH

Neem (Azadirachta Indica A. Juss) Capsules for Prophylaxis of COVID-19 Infection: A Pilot, Double-Blind, Randomized Controlled Trial

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ABSTRACT

Context • SARS-CoV-2 is a global public-health concern. Interventions to prevent infection are urgently needed. The anti-inflammatory and antiviral effects of neem make it a potential agent for COVID-19 prophylaxis.

Objective • The study intended to evaluate the prophylactic effects of neem capsules for persons at high risk of COVID-19 infection due to contact with COVID-19 positive patients.

Design • The research team designed a prospective, randomized, double-blind, placebo-controlled, parallel-design study.

Setting • The study was conducted at a single center in India.

Participants • Participants were 190 healthcare workers at the hospital or relatives of patients with COVID-19 infection.

Intervention • Of the 190 participants, 95 were in the intervention group and 95 in the control group. Participants received 50 mg of a proprietary, patent-pending, neem-leaf extract or a placebo orally in capsules, twice a day for 28 days.

Outcome Measures • The number of individuals positive for COVID-19 between baseline and follow-up on day 56 was the primary outcome measure. Secondary measures included an evaluation of neem's safety and its effects on quality of life (QOL) and changes in biomarkers.

Results • The mean age of participants was 36.97 years, and 68.42% were male. Total 13 subjects tested positive during the study. All were asymptomatic. Of the 154 participants who completed the study *per-protocol*, 11 tested positive, 3 in the intervention group and 8 in the control group. The probability of COVID-19 infection in participants receiving the intervention was 0.45 times that of participants receiving the placebo, a relative risk of 0.45, with the effectiveness of the intervention being around 55%. Treatment-emergent adverse events (TEAEs) in both groups were minimal and were of grade 1 or 2 in severity. Biomarkers and QOL remained stable in both groups.

Conclusions • The study found a reduced risk of COVID-19 infection in participants receiving neem capsules, which demonstrates its potential as a prophylactic treatment for the prevention of COVID-19 infection. The findings warrant further investigation in clinical trials. (*Altern Ther Health Med.* [E-pub ahead of print.])

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic and is a cause of global public-health concern. By the beginning of 2021, over 100-million cases and more than two-million deaths had been reported worldwide.[1] The SARS-CoV-2 infection has been found to be both highly contagious and 5-to-50-fold more lethal than seasonal influenza, with an estimated mortality rate of 0.5-5%.[2] Interventions to prevent COVID-19 are urgently needed.

Healthcare workers (HCW), people involved in essential services, and relatives of patients with COVID-19 are at increased risk due to the rapid transmission of SARS-CoV-2. Preventive options such as social distancing, hand washing, and wearing masks are suggested and used to reduce the risk of the infection. Additionally, use of hydroxychloroquine (HCQ) chemoprophylaxis, which not only has limited

efficacy but also has serious side effects, is recommended.[3] In addition to these preventive measures, multivitamins are recommended to boost immunity.

For centuries, Ayurveda has provided safe, accessible, affordable, and simple preventive measures for various diseases, such as medicated water, gargling, oil pulling, nasal administration of oils, and Rasayana. In the current pandemic, various ayurvedic preparations are being used for their beneficial effects on immunity; a large number are also being tested for the treatment of COVID-19 infection.[4]

The neem (Azadirachta indica A. Juss) is an abundantly available tree, the products from which have been widely used as a traditional medicine for many centuries in tropical countries. It is known to contain bioactive molecules with anti-inflammatory[5] and antiviral properties.[6-8] Early studies have shown that neem extracts, at an initial step of viral genome replication, can significantly inhibit polio, human immunodeficiency virus (HIV), dengue fever, and the coxsackie B group of viruses.[6-8]

Recently, molecular docking studies on influenza virus have clearly identified the binding site of neem compounds on conserved residues of influenza virus nucleoprotein[9,10] and also identified the putative mechanism of its antiviral activity.

Additionally, several classical texts mention that neem has antimicrobial properties (Jantughna/Krimighna) and is useful for intermittent fevers (Vishama jwara). Neem leaves have also been reported to remove toxins, purify blood, and prevent damage through its medicinal properties.[11]

Neem's anti-inflammatory and antiviral effects make it a potential agent for use in COVID-19 prophylaxis. The current study was undertaken to evaluate the prophylactic effects of neem capsules for persons at high risk of COVID-19 infection due to contact with COVID-19 positive patients. Its secondary objectives were assessing the safety of the neem capsules and their effects on quality of life (QOL) and biomarkers.

METHODS

The study was approved by the Institutional Ethics Committee and registered at CTRI (CTRI/2020/07/026560). The study was conducted in accordance with International Council for Harmonization's Good Clinical Practice (GCP) guidelines (ICH E6 [R2]), the current revision of the Declaration of Helsinki, and all applicable local regulatory and ethical requirements. Written informed consent was received from all participants prior to enrollment in the study. Nisarga Biotech in Maharashtra, India sponsored the study.

Participants

This was a pilot, prospective, randomized, double-blind, placebo-controlled, parallel-design study. Participants were persons coming in contact with COVID-19 patients. The study was conducted at a single center, the ESIC Medical College and Hospital in Faridabad, India.

Participants were male and female healthcare workers, such as physicians, nurses, chemists, pharmacists, stretcher-bearers, respiratory therapists, and administrative staff, who work at the hospital, or relatives of patients with COVID-19 infection. All the potential participants were contacted telephonically and informed about the study.

Participants were included in the study if they: (1) were aged 18 to 60 years; (2) agreed not to self-medicate with chloroquine, hydroxychloroquine, or other potential antivirals; (3) had not been previously diagnosed with COVID-19; (4) were not currently symptomatic with an acute respiratory infection; (5) agreed to use contraceptive methods; and (6) agreed to comply with the trial and follow-up procedures.

Participants were excluded from the study if they: (1) had a known hypersensitivity to neem products; (2) were on other prophylactic medications; (3) had a suspected or confirmed COVID-19 infection, defined as a temperature >38° C, a cough, shortness of breath, and sore throat; (4) had positive confirmatory testing for COVID-19; (5) had suspected or confirmed convalescent COVID-19, defined as any of the above symptoms within the 4 weeks to the start of the study; or (6) were on angiotensin-converting enzyme (ACE) inhibitor.

Procedures

Potential participants were consented and evaluated for protocol specified inclusion/exclusion criteria based on demographic, medical history, prior medications and laboratory assessments. Eligible participants started study treatment on day 1 for next 28-days. The participants were instructed to visit the study center postintervention on day 29, at follow up visit on day 56 and anytime if they develop symptom of COVID-19 or experience any adverse event. Compliance to the study treatment was measured on day 29. All the data were captured in eCRF.

Randomization and blinding

Participants were allocated randomly to one of the two groups in a 1:1 ratio in double-blinded fashion. A sponsor-designated statistician generated a computerized randomization list. A simple, static, randomization scheme was used to allocate participants to the study's two groups, an intervention and a control group. The study's medications were packed in bottles and were dispensed sequentially to the participants based on the randomization sequence.

Concomitant and prohibited medication

Participants could take their concomitant medication for any comorbid diseases, but they couldn't take any other prophylactic medications for COVID-19, such as chloroquine, hydroxychloroquine, or other potential antivirals. Other herbal preparations or medications which in the opinion of the investigators could confound the efficacy of neem, weren't allowed during the trial. Participants were instructed to inform the research team if they took any concomitant medications during the study.

Compliance

Compliance was assessed based on the amount of the study's intervention or placebo that was dispensed and consumed by participants or returned at a subsequent visit. A compliance rate lower than 80% was defined as poor compliance. Participants were encouraged to comply with the treatment regimen and were instructed to return their unused capsules to designated personnel at their next visit.

Outcome measures

The primary outcome measure was the number of participants who tested positive for COVID-19 between baseline and follow-up on day 56. All treatment-emergent adverse events (TEAE), regardless of seriousness or relationship, were recorded. QOL was assessed, and biomarkers—interleukin-6 (IL-6), immunoglobulin G (IgG), immunoglobulin M (IgM), and C-reactive protein (CRP)—were evaluated.

Intervention

The intervention in the current study—Nisarga Biotech's proprietary, patent-pending, neem-leaf extract—was formulated in the form of capsules and contains active metabolites, particularly nimbolide, nimbin, and salannin.[12] The formulation offers safety and tolerability, as confirmed by single-dose, good laboratory practice (GLP) toxicity studies in mice and rats, at doses of up to 2000 mg/kg and by a 28-day GLP toxicity study in rats at a dose of 1000 mg/kg.[12]

Participants received 50 mg capsules orally—either neem or a placebo—twice a day for 28 days. The capsules were self-administered with water and were taken at approximately the same time each day. The enrolled participants were followed for a period of 56 days, with 28 days being the treatment period and the following 28 days being the follow-up.

Assessments

Efficacy assessment. Testing of each participant, using a 2019-nCoV, reverse transcription polymerase chain reaction (RT-PCR) test, occurred at baseline and postintervention on day 29. In addition, an RT-PCR test was also performed for participants who showed signs of COVID-19 infection during the study, such as fever, cough, or breathlessness.

Safety assessment. The assessment occurred from the first dose of the study's intervention or placebo until 30 calendar days after the last dose was recorded. All adverse events resulting in discontinuation from the trial were followed until resolution or stabilization. Safety parameters included TEAEs, serious adverse events (SAEs), assessment of vital signs, physical examination, and laboratory parameters, including hematology, biochemistry, and ECGs. The causality assessment was categorized as related or not related, and severity was graded using National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE), V5.0.

QOL assessment. QOL was assessed using the World Health Organization's (WHO's) quality of life (WHO-QOL) questionnaire, at baseline, postintervention on day 29, and at follow up on day 56.

Biomarker assessment. Biomarker analysis occurred at baseline and postintervention on day 29.

Statistical Analysis

Statistical analysis included analysis of quantitative variables using summary statistics—mean and standard deviation—and of qualitative variables using numbers and percentages. T-tests were performed for within- and between-group comparison. *P* values of $< .05$ were considered to be statistically significant.

Participants who received at least one dose of the intervention or placebo were included in the safety analyses. Participants who had RT-PCR testing post-randomization and who received >80% of the intervention or placebo were considered in the per-protocol (PP) analyses, and participants who received at least one dose of the intervention or placebo and who had undergone RT-PCR COVID-19 testing post-randomization were considered in the modified intent-to-treat (mITT) analyses.

Efficacy was calculated from the number of participants who tested positive for COVID-19. Other end points were the number of participants with severe respiratory COVID-19 infection and changes in QOL. Safety analysis included incidence of TEAEs and related TEAEs and incidences of grades 3 or 4 TEAEs, SAEs, and death.

The sample size of 200 participants was considered to be adequate to understand a preliminary prophylactic effect of the intervention. Considering that 25% of enrollees would likely be dropouts, 250 participants were to be enrolled in the study. However, the recruitment was called off after enrolling 190 participants due to a lower-than-expected recruitment rate.

RESULTS

Participants

A total of 255 potential participants consented to be screened for the study between August and December 2020. Of those, 23 potential participants withdrew consent during the screening, and 42 failed screening—20 tested positive for RT-PCR, 17 tested positive for COVID-19 antibodies, and 5 met other exclusion criteria.

The study enrolled 190 eligible participants, 95 each in the intervention and placebo groups. Out of 95 participants enrolled in each group, 70 (73.7%) participants in the intervention group and 83 (87.4%) in the placebo group completed the study (Table 1).

Demographics

The mean age of participants was 36.97 years; 37.05 years in the intervention group and 36.89 years in the placebo group. The study enrolled a preponderance of males (68.42%). Most participants had no major medical history and no significant prior medication history. Six participants in the intervention group had a medical history of hypertension, diabetes, PCOD, or renal calculi, whereas four participants in

Table 1. Participant Flow

Category	Intervention Group N	Control Group N	Total N
Participants consented	-	-	255
Participants withdrawing consent during screening	-	-	23
Individuals failing screening	-	-	42
Participants positive on RT-PCR COVID-19 test	-	-	20
Participants positive for COVID-19 antibodies			17
Participants meeting exclusion criteria	-	-	5
Participants randomly assigned to a group	95	95	190
Participants completing the study	70	83	153
Participants discontinuing participation during the study	25	12	37
Participants testing positive early on RT-PCR Covid-19 test	2	1	3
Participants lost to follow-up	12	5	17
Participants withdrawing consent	8	6	14
Participants with poor compliance	2	0	2
Other [UPT +ve]	1	0	1

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; UPT, urine pregnancy test.

Table 2. Efficacy Assessment (n = 154)

Test results	Intervention Group N (%)	Control Group N	Total N
Participants with RT-PCT positive result	3 (4.3)	8 (9.5)	11
Participants with RT-PCT negative result	67 (95.7)	76 (90.5)	143
Total participants	70	84	154
	Relative risk		0.45
	Effectiveness		55.00%

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction.

the placebo group had a medical history of hypertension. Four participants in each group had received at least one prior medication. Most of the prior medication were antidiabetic or anti-hypertensive.

Compliance

The mean number of capsules consumed in the intervention group was 49.13 and in the placebo group was 55.03. Overall, treatment compliance was good. Of the 190 participants, 154 (81.05%) participants consumed >80% of the supplied capsules, and 34 (17.89%) participants consumed <80% of the supplied capsules. For two participants, information on capsule consumption couldn't be retrieved.

Efficacy

For the PP analysis, data for 154 participants were considered evaluable for analysis. Out of the 154 participants, 70 were in the intervention group and 84 in the placebo group. Two participants, who had a positive RT-PCR testing but <80% compliance, were not considered for analysis. Three of the 70 participants in the intervention group and 8 of the 84 participants in the control group tested positive for COVID-19 between baseline and follow-up on day 56.

The results showed that the probability of COVID-19 infection in participants receiving the intervention was 0.45 times that of participants receiving the placebo, with a relative risk of 0.45. The results indicate the effectiveness of the intervention to be around 55% (Table 2).

In the mITT analysis, which was based on 156 participants—including the two positive participants on the RT-PCR who had been excluded from the PP analysis—the relative risk of COVID-19 infection in participants who were receiving the intervention was 0.73 times that of those who were receiving the placebo.

All 13 participants who tested positive for COVID-19 were asymptomatic; no severity comparison could be performed.

Safety

Of the 190 participants, 8 (4.2%) participants developed 17 TEAEs, 5 (5.3%) participants in the intervention group reported 9 TEAEs, and 3 (3.2%) participants in the control group reported 8 TEAEs (Table 3). Fourteen TEAEs in 7 (3.6%) participants were treatment related; 6 of those related TEAEs were in the intervention group and 8 in the control group (data not shown).

Table 3. Summary of TEAEs by System Organ Class and Preferred Term (n=190)

	Intervention Group		Control Group		Total	
System Organ Class, Preferred Term	N (%)	Number of Events	N (%)	Number of Events	N (%)	Number of Events
At least one TEAE	5 (5.3)	9	3 (3.2)	8	8 (4.2)	17
Gastrointestinal Disorders						
Reduced appetite	2 (2.1)	2	1 (1.1)	1	3 (1.6)	3
Bad taste	1 (1.1)	1	-	-	1 (0.5)	1
Abdominal distention	1 (1.1)	1	1 (1.1)	1	2 (1.1)	2
Bloating	1 (1.1)	1	-	-	1 (0.6)	1
Abdominal pain	1 (1.1)	1	-	-	1 (0.6)	1
Irregular bowel habits	1 (1.1)	1	-	-	1 (0.6)	1
General Disorders and Administration Site Conditions						
Heaviness in head	-	-	1 (1.1)	1	1 (0.6)	1
Laziness	-	-	1 (1.1)	1	1 (0.6)	1
Musculoskeletal and connective tissue disorders						
Leg pain	-	-	1 (1.1)	1	1 (0.5)	1
Nervous system disorders						
Anxiety	1 (1.1)	1	-	-	1 (0.6)	1
Disturbed sleep pattern	1 (1.1)	1	1 (1.1)	1	2 (1.1)	2
Drowsiness	-	-	1 (1.1)	1	1 (0.6)	1
Headache	-	-	1 (1.1)	1	1 (0.6)	1

Abbreviations: TEAE, treatment emergent adverse events

All the reported TEAEs were grade 1 or grade 2 in severity. None of the participants received concomitant treatments for TEAEs. Gastrointestinal TEAEs were common in participants of intervention group, whereas TEAEs related to general disorders were common in the control group.

None of the participants developed severe or serious TEAEs. One participant had a treatment interruption and a dose reduction. No significant changes were observed in vitals, hematology, biochemistry, or ECGs in either group.

Biomarkers

No apparent changes were noted for either group in biomarkers postintervention on day 29 as compared to baseline, except a statistically significant increase in the IgG levels in the intervention group, with $P = .02$, and in C reactive protein in the control group, with $P = .01$ (Table 4). Similarly, no significant differences occurred in the biomarker levels between the intervention and the control groups.

Quality of Life

QOL scores remained stable in both the groups over the three visits and were comparable in the two groups (Table 5). At postintervention on day 29, two participants in the intervention group reported improved sleep and appetite; and one participant reported improved sleep. At follow-up on day 56, two participants in the intervention group reported improved appetite, two reported improved sleep, two others reported increased work efficiency, and one reported relief from stress.

DISCUSSION

Number of treatments are being evaluated for the prophylaxis of COVID-19 in clinical studies across the world. The key conclusion from completed studies seems to be that HCQ is not much effective. There is little evidence regarding other compounds, with all RCTs using treatments other than HCQ still ongoing.[13]

The current study has confirmed the prophylactic activity of the intervention. The probability of COVID-19 infection in participants receiving the intervention was 0.45 times of those participants who received placebo capsules. Thus, indicating the effectiveness of the intervention of around 55%.

In prophylaxis study of hydroxychloroquine in 132 participants, there was no significant difference in infection rates in participants randomized to receive hydroxychloroquine compared with placebo (4 of 64 [6.3%] vs 4 of 61 [6.6%]; $P > .99$). In this study, there was no clinical benefit of hydroxychloroquine administered daily for 8 weeks as pre-exposure prophylaxis in hospital-based HCWs exposed to patients with COVID-19.[14] In the second study of hydroxychloroquine in 1483 healthcare workers, the incidence of Covid-19 was 0.27 events per person-year with once-weekly and 0.28 events per person-year with twice-weekly hydroxychloroquine. These results were comparable with 0.38 events per person-year with placebo.[15]

The mechanism by which neem reduces the rate of infection is not completely known, but it could be due to its anti-inflammatory and antiviral activity, as demonstrated by some preclinical studies in which a neem extract has shown

Table 4. Summary of Biomarkers.

Biomarkers		Baseline		Postintervention (day 29)	
		Intervention Group	Control Group	Intervention Group	Control Group
IL-6	n	95	95	70	83
	Mean ± SD	14.52 ± 18.68	14.93 ± 20.28	13.16 ± 15.97	14.24 ± 19.67
	Range	0-112	0-112.9	0.1-70.4	0-112
	P value between groups	.88		.70	
	P value within groups, baseline to postintervention			.14	.98
IgG	n	95	95	70	83
	Mean ± SD	0.06 ± 0.42	0.44 ± 3.09	0.78 ± 2.61	0.89 ± 2.86
	Range	0-3.96	0-29.4	0-12.3	0-15.9
	P value between groups	.22		.79	
	P value within groups, baseline to postintervention			0.02[#]	0.41
IgM	n	95	95	69	83
	Mean ± SD	0.12 ± 0.66	1.36 ± 7.54	1.72 ± 9.86	2.71 ± 11.44
	Range	0-4.43	0-63.36	0-65.1	0-80.1
	P value between groups	.11		.56	
	P value within groups, baseline to postintervention			.18	.43
C-reactive Protein	n	95	95	71	82
	Mean ± SD	0.55 ± 0.45	0.52 ± 0.09	0.6 ± 0.26	0.55 ± 0.09
	Range	0-4.8	0.5-1.4	0.5-2.7	0.5-1.2
	P value between groups	.52		.17	
	P value within groups, baseline to postintervention			.39	.01[a]

[a]Indicates a significant change between baseline and postintervention for the group.

Note: For between group comparisons, the study used the applied t-test for independent samples, and for within group comparisons, it used the applied paired t-test for pre-post comparisons.

Abbreviations: IL-6, interleukin-6; IgG, immunoglobulin G; IgM, immunoglobulin M; SD, standard deviation.

Table 5. Quality of Life.

Quality of Life		Intervention Group	Control Group
Baseline	n	95	95
	Mean ± SD	80.98 ±5.52	80.29 ± 6.61
	Range	67-91	64-92
	P value		
	Between groups	.43	
Postintervention on day 29	n	70	83
	Mean ± SD	80.96 ± 5.57	80.33 ± 6.31
	Range	67-91	64-92
	P value		
	Between groups	.51	
	Within a group (change from baseline)	.35	.06
Follow-up on day 56	n	69	83
	Mean ± SD	81.07 ± 5.63	80.39 ± 6.20
	Range	67-91	65-92
	P value		
	Between groups	.47	
	Within a group (change from baseline)	.07	.04[a]

[a]Indicates a significant change between baseline and postintervention for the group.

Note: For between group comparisons, the study used the applied t-test for independent samples, and for within group comparisons, it used the applied paired t-test for pre-post comparisons.

Abbreviations: SD, standard deviation.

significant attenuation of circulating inflammatory cytokines—including nuclear factor-kappa B (NFkB), cyclooxygenase-2 (COX2), interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ)—and antiviral effects against multiple viruses.[6-8,16]

As a proof-of-concept study, the current study considered both the mITT population—participants who received at least one dose of the intervention and who had an RT-PCR test between baseline and follow-up—and the PP population—participants who took >80% of the intervention dosages and had a RT-PCR test between baseline and follow-up. Moreover, study results mainly focused on per protocol analysis to ensure that conclusions are drawn on the patients taking adequate treatment during the study.

Neem leaf extracts are used in Ayurveda for many ailments, such as for chronic fever, chronic ulcers, and skin-related diseases, such as eczema and psoriasis. They have been used long term without any major safety concerns. In rats and mice, neem leaf extracts have been evaluated in acute oral toxicity studies at doses up to 5000 mg/kg body weight[17-18] and in 28-day, repeated-dose oral toxicity studies at doses up to 1000 mg/kg body weight,[17,19] with no significant findings. This supports the notion that neem leaf extracts are well tolerated. In a recently concluded study with diabetes patients, doses of 125 mg, 250 mg, and 500 mg of neem extract or a placebo were given twice daily for 12 weeks. The study found no significant changes in vital, hematological, renal, or hepatic functions, which further supports long-term use of neem leaf extracts.[20]

The study also indicated that neem capsules given at a dose of 50 mg twice a day were safe and well tolerated in participants who have a high risk of COVID-19 infection. The reported TEAEs were mild to moderate in severity, and all events well resolved without medication. The need for drug interruption and dose reduction was minimal. The safety of the intervention was in line with that in the published literature.[20-22]

Statistically significant changes were noted in IgG level between baseline and postintervention on day 29 in the intervention group and C-reactive protein in the placebo group. These changes weren't considered to be relevant due to the high variability in the data, and they were clinically insignificant.

Overall, the results are encouraging and offers a low-cost, safer alternatives for prophylaxis in this global COVID-19 crisis. However, the results require cautious interpretation. In the absence of the statistical power required to draw a strong conclusion, the findings of this early signal-seeking study need to be verified in a larger population study. The number of dropouts due to various reasons is the other limitation of the study.

CONCLUSIONS

The substantially reduced risk of COVID-19 infection in participants receiving the neem capsules in the current study demonstrated its potential as a prophylactic treatment for the prevention of COVID-19 infection. A randomized, double blind study with a larger number of participants is warranted to substantiate these findings. Treatment can also be developed as a therapeutic intervention for COVID-19 infection, considering the possible anti-inflammatory and antiviral activity of neem capsules.

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