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An Open-Labelled Randomized Clinical Trial to evaluate the efficacy of Siddha drug - *Vettummaaran Kuligai* with *Nilavembu Kudineer* (VMK-NVK) in the Management of Mild to Moderate COVID-19 (SARS-CoV2 infection)

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ABSTRACT:

COVID-19, caused by SARS-CoV-2, posed an unprecedented global health challenge. There was a growing interest in identifying safe and effective Siddha formulation for the management of COVID-19, and hence the study to evaluate the efficacy of *VettummaaranKuligai* with *NilavembuKudineer* (VMK-NVK) in comparison with Ivermectin was explored. COVID-19, caused by SARS-CoV-2, prompted the search for safe and effective Siddha formulations. This open-labelled, randomized case-control clinical trial evaluated the efficacy of *Vettummaaran Kuligai* with *Nilavembu Kudineer* (VMK-NVK) compared to Ivermectin in mild to moderate COVID-19 patients. Sixty RT-PCR confirmed cases were randomized into two groups: Group A received VMK-NVK (*Nilavembu Kudineer* 60 mL with *Vettummaaran Kuligai* 1 pill twice daily for one week), and Group B received Ivermectin (12 mg/day for 5 days). Clinical assessment was conducted daily, with RT-PCR and laboratory investigations performed weekly. Results showed that VMK-NVK demonstrated non-inferior efficacy to Ivermectin in achieving RT-PCR negativity, with complete viral clearance by day 14 in both groups. Symptom resolution and clinical recovery were comparable. VMK-NVK showed greater reduction in inflammatory markers (IL-6 and CRP), indicating superior anti-inflammatory effects, while both groups had significant reduction in D-dimer levels. No adverse effects were observed, and safety parameters remained normal. In conclusion, VMK-NVK is a safe, affordable, and evidence-based alternative for managing mild to moderate COVID-19, warranting further large-scale, double-blind studies.

KEYWORDS: COVID-19, Ivermectin, *Nilavembu Kudineer,* SARS-CoV-2, Siddha, *Vettummaaran Kuligai*.

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1. INTRODUCTION:

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has had an unparalleled global impact on public health, economies, and societies. Since its emergence in December 2019, the virus has infected over 760 million individuals and resulted in millions of deaths worldwide, making it one of the most devastating pandemics in modern history. [1].In India, COVID-19 exerted significant strain on healthcare systems, with high hospitalization rates and economic losses due to widespread morbidity and productivity decline. The financial burden associated with diagnostics, hospital admissions, and pharmacotherapy has been substantial, particularly for lower- and middle-income groups [2].

While vaccination campaigns and antiviral drugs have mitigated severe disease, challenges persist in the effective management of mild to moderate cases, particularly with the emergence of new viral variants and the limitations of available drugs[3]. Many synthetic antivirals and repurposed agents such as Ivermectin, Favipiravir, and Remdesivir presented mixed efficacy outcomes and considerable cost implications[4,5]. This scenario has prompted renewed interest in affordable, safe, and evidence-based traditional medicine systems.

The Siddha system of medicine, one of India's oldest indigenous medical traditions, has historically demonstrated success in managing epidemic fevers such as Dengue, Chikungunya, and Influenza[6,7]. Siddha formulations like *Nilavembu Kudineer* (NVK) have shown antiviral and immunomodulatory activities through inhibition of viral replication and cytokine modulation[8]. *Vettummaaran Kuligai* (VMK), described in Siddha classics, is also renowned for its antipyretic and detoxifying properties[9]. Combining VMK with NVK (VMK–NVK regimen) represents an innovative, cost-effective approach rooted in traditional pharmacology and modern clinical rationale.

During the early phase of the COVID-19 pandemic, Ivermectin emerged as one of the most widely used repurposed drugs globally due to its reported antiviral effect against RNA viruses and its ability to inhibit SARS-CoV-2 replication in vitro. Multiple national task forces (including in India) permitted its off-label use for mild to moderate COVID-19 cases during the period of this trial, and Ivermectin was included in interim treatment advisories in several countries because it was inexpensive, widely available, and had an established safety profile. [10] Therefore, Ivermectin served as a rational comparator drug for this study, as it represented the commonly accepted standard of care in clinical practice at that time. Comparing VMK-NVK to Ivermectin thus allowed a more meaningful and pragmatic evaluation of whether Siddha therapy could match or exceed the therapeutic effects of a real-world treatment option being used during active pandemic management

From a national and global perspective, such integrative research offers dual benefits—strengthening indigenous healthcare systems and contributing to the global search for safe, economical therapeutic strategies against viral pandemics. The cost of Siddha formulations like VMK–NVK is considerably lower compared to modern antiviral drugs, enhancing accessibility in community healthcare settings.

The primary challenge lies in bridging the gap between traditional empirical evidence and modern clinical validation. This research aims to overcome these challenges by adopting rigorous scientific methodology to evaluate the efficacy and safety of VMK–NVK in mild to moderate COVID-19 cases. The study introduces a novel evidence-based framework integrating Siddha formulations into contemporary medical management.

The central theme of this research is the validation of a Siddha polyherbal-mineral combination (VMK–NVK) through modern clinical protocols to demonstrate its immunomodulatory and antiviral potential. The study provides innovative insights into how traditional medicine can complement modern therapeutics in pandemic management, closing the existing gap between ancient knowledge and scientific validation.

Based on the literature, improving viral management requires multidimensional strategies—targeting inflammation, immune modulation, and viral replication simultaneously. VMK–NVK's diverse phytochemical and mineral composition enables multi-target action. Literature on its constituent herbs—such as *Andrographis paniculata* and *Piper longum*—supports their roles in cytokine suppression, antioxidant enhancement, and antiviral activity. [8,11,12] This research proposes that integrating VMK–NVK as an adjunct therapy could reduce disease duration and inflammatory load while maintaining cost efficiency.

1.1. Objectives:

1. To assess the therapeutic efficacy of VMK-NVK compared to Ivermectin in mild to moderate COVID-19 patients.
2. To evaluate the effect of VMK-NVK on clinical outcomes, RT-PCR conversion, and inflammatory biomarkers.
3. To determine the safety and tolerability of VMK-NVK under controlled clinical settings.

2. MATERIALS AND METHODS

2.1. Study Design and Setting:

An open-labelled randomized clinical trial was conducted to evaluate the efficacy and safety of the Siddha drug combination VettummaaranKuligai with NilavembuKudineer (VMK-NVK) in the management of mild to moderate COVID-19 infection. The study was carried out at the Government Siddha Medical College & Hospital, Palayamkottai, in collaboration with Tirunelveli Medical College Hospital, Tamil Nadu, from May 2021 to February 2022. Institutional Ethics Committee approval (Ref. No. 1795/SIDDHA/2020, dated 09.10.2020) was obtained prior to the commencement of the trial, and the

study was registered with the Clinical Trials Registry of India (CTRI/2020/11/038210).

2.2. Sample Size and Sampling techniques

A total of 60 patients diagnosed with mild to moderate COVID-19 infection by RT-PCR were recruited and randomized equally (1:1 ratio) into two groups—Group A (VMK-NVK) and Group B (Ivermectin). Convenient Sampling technique was used. Informed written consent was obtained from all participants. A minimum sample size of 30 per group was considered statistically valid based on earlier Siddha clinical trials with a standard deviation of ±5% for mean differences in clinical improvement[8].

2.3. Inclusion Criteria

- Adults aged 18–70 years.
- Laboratory-confirmed SARS-CoV-2 infection via RT-PCR.
- Mild to moderate clinical symptoms (fever, cough, malaise, anosmia, myalgia).
- Ability to provide informed consent and comply with study procedures.

2.4. Exclusion Criteria

- Severe or critical COVID-19 cases requiring mechanical ventilation.
- Pregnant or lactating women.
- Patients with major comorbidities (diabetes, renal, hepatic, or cardiac disorders).
- Immunocompromised individuals or those on immunosuppressive therapy.
- Participation in another investigational drug trial within the past 30 days.

2.5. Source of Drug and Material Procurement

Vettummaaran Kuligai and *Nilavembu Kudineer* were procured from the GMP-certified pharmacy of the Government Siddha Medical College, Palayamkottai. Raw herbal materials were authenticated by the Department of Gunapadam, and the formulations were prepared following the classical Siddha text *Agasthiyar Kuligai Kothu 60*. Ivermectin tablets (12 mg) were procured from a standard pharmaceutical company approved by the Tamil Nadu Medical Services Corporation (TNMSC). All laboratory investigations were conducted at the Department of Pathology, Tirunelveli Medical College.

2.6. Intervention and Treatment Protocol

- **Group A (Siddha Intervention):***Nilavembu Kudineer* (60 mL decoction) with *Vettummaaran Kuligai* (65 mg tablet) administered orally twice daily after food for 7 days.
- **Group B (Standard):** Ivermectin 12 mg once daily for 5 consecutive days.

  Both groups received standard dietary and symptomatic care as per national COVID-19 treatment guidelines (MoHFW, 2021).

Follow-up assessments were conducted on Day 0, Day 7, and Day 14.

2.7. Clinical and Laboratory Assessments

Baseline data included demographic profile,comorbidity assessment. Clinical evaluation parameters were temperature, oxygen saturation (SpO_2), respiratory rate. Laboratory investigations included:

- Complete blood count (CBC)
- Liver function tests (LFT)
- Renal function tests (RFT)
- C-reactive protein (CRP)
- D-dimer
- Interleukin-6 (IL-6)
- Serum ferritin
- Lactate dehydrogenase (LDH)
- RT-PCR cycle threshold (CT) values for SARS-CoV-2 detection
- CT-chest

All laboratory investigations were performed using standardized diagnostic kits and validated procedures. The RT-PCR testing was performed at a NABL-accredited laboratory using the TaqMan-based real-time detection system (Thermo Fisher Scientific, USA). Biochemical estimations were done using an automated analyzer (Erba XL-640) calibrated before each run.

2.8. Outcome Measures

- **Primary Outcome:**Negative RT-PCR conversion for SARS-CoV-2.
- **Secondary Outcomes:** Reduction in clinical symptoms, normalization of biochemical markers (CRP, IL-6, D-dimer, Ferritin, LDH), and overall recovery rate by Day 14.

Safety parameters included liver and kidney function test results and the recording of adverse drug reactions, if any.

2.9. Data Recording and Monitoring

All data were documented in pre-validated case report forms (CRFs). Regular telephonic and in-person follow-ups ensured patient adherence. A data safety monitoring committee reviewed the trial's progress and adverse events, if reported.

2.10. Statistical Analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Between-group comparisons were performed using the independent sample t-test for parametric data and the Mann–Whitney U test for non-parametric data. Categorical data were analyzed using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Study Population

A total of 60 participants meeting the inclusion criteria were enrolled and randomized equally into two groups: Group A (VMK-NVK) and Group B (Ivermectin). All 60 participants

completed the trial. There were no protocol deviations or drop outs.

3.2. Demographic Profile (Table 1)

The mean age of the study population was 38.07 ± 17.7 years in the Siddha group and 48.03 ± 16.0 years in the Ivermectin group. Males predominated in the Ivermectin group (73.3 %), whereas females were slightly higher in the Siddha group (53.3 %). Most participants belonged to the lower-middle socioeconomic class. Baseline vitals, oxygen saturation were comparable between the groups ($p > 0.05$).

3.3. Clinical Characteristics (Tables 2& 3)

By the 7thday of treatment, a significant improvement in clinical symptoms was noted in both study groups. Patients in the Ivermectin group(Group B) demonstrated a faster rate of recovery, with 96.7% becoming asymptomatic, and only a small number continuing to experience mild fever, cough, or breathing difficulty. In comparison, 63.3% of patients in the Siddha medication group(Group A) had become asymptomatic by Day 7, while a few still reported mild fever (20%), breathlessness (20%), and loss of taste (16.7%).

By Day 14, 90% of patients in the Siddha Medication group(Group A) achieved complete symptom resolution, with only isolated cases of mild residual symptoms. The Ivermectin group(Group B) maintained 96.7% asymptomatic status by this point, indicating faster initial improvement but comparable overall recovery between the two treatment groups by the end of the observation period.Overall, both treatment groups showed significant improvement in clinical symptoms over time, with Ivermectin demonstrating an earlier symptomatic relief by Day 7, while Siddha medication achieved comparable recovery by Day 14.

3.4.RT-PCR Conversion (Table 4& 5)

RT-PCR negativity was achieved by Day 7 in 93.3 % of VMK-NVK participants and 96.7 % of Ivermectin participants, and all patients tested negative by Day 14. P value(0.5536) greater than 0.05 indicates that there is no significant statistical difference between the two treatment groups.Both treatments performed similarly in the trial. Mean CT values significantly increased from 19.07 ± 2.15 to 30.5 ± 0.51 in both groups ($p < 0.0001$), indicating a marked reduction in viral load. There is a statistically significant increase in CT value of both groups after7days.

3.5. Laboratory Outcomes (Tables 6&7)

A consistent decline was observed in inflammatory and biochemical markers across both groups Both treatments led to a highly significant reduction in CRP levels (P-value <0.0001). The Ivermectin group achieved a slightly greater overall reduction in the mean CRP level by Day 14 (3.01) compared to the Siddha Medication group (3.10).Ivermectin showed superior efficacy because the reduction in LDH was highly statistically significant (P-value <0.0001).

The reduction in the Siddha Medication group was not statistically significant (P-value = 0.064).Ivermectin achieved a lower final mean Ferritin level (51.56), making it superior in absolute reduction of this marker compared to the Siddha Medication group (65.09).Both treatments demonstrated a statistically significant reduction (P-values 0.003 and 0.011).Siddha Medication was superior, resulting in a slightly lower final mean IL-6 level of 4.73compared to the Ivermectin group (6.04).Both treatments showed a highly significant reduction in IL-6 (P-value <0.0001 for both).The Siddha Medication group's final mean (144.00) was only marginally lower than the Ivermectin group's final mean (144.77). Both groups achieved a near-identical and significant reduction in D Dimer levels.

3.6. Safety Evaluation

No adverse drug reactions or intolerances were reported in either group. Liver and renal function test (Table 5 & 6) results remained within normal limits throughout the study. Vital parameters were stable, and no serious adverse events occurred.

Table 1: Distribution of patient's demographic details

Demographic details		Group			
		Group A		Group B	
		N	N%	N	N%
Age group(years)	<20	8	26.7%	2	6.7%
	21-30	8	26.7%	5	16.7%
	31-40	0	0.0%	2	6.7%
	41-50	4	13.3%	6	20.0%
	51-60	7	23.3%	9	30.0%
	>61	3	10.0%	6	20.0%
Gender	Female	16	53.3%	8	26.7%
	Male	14	46.7%	22	73.3%
Marital Status	Married	19	63.3%	25	83.3%
	Unmarried	11	36.7%	4	13.3%
	Widow	0	0.0%	1	3.3%
Educational Status	Illiterate	1	3.3%	6	20.0%
	Read&write	29	96.7%	14	46.7%
	Readandwrite	0	0.0%	10	33.3%
Present Occupation	Desk work	17	56.7%	10	33.3%
	Fieldworkwith physicallabour	5	16.7%	13	43.3%
	Housewife	8	26.7%	7	23.3%
Socio-economic Status	AbovePovertyline	27	90.0%	20	66.7%
	Belowpovertyline	3	10.0%	10	33.3%

Habitat	**Rural**	2	6.7%	5	16.7%
	Semiurban	6	20.0%	8	26.7%
	Urban	0	0.0%	1	3.3%
	Urban	22	73.3%	16	53.3%
Religion	**Christian**	2	6.7%	3	10.0%
	Hindu	27	90.0%	24	80.0%
	Muslim	1	3.3%	3	10.0%
Co-Morbidities	**Nil**	30	100.0%	30	100.0%

Table 2: Comparison of Clinical Characteristics between Group A and Group B from Day 0 to Day 7

Symptom	**Day 0 Group A (N %)**	**Day 0 Group B (N %)**	**Day 7 Group A (N %)**	**Day 7 Group B (N %)**	**Day 14 Group A (N %)**	**Day 14 Group B (N %)**
Asymptomatic	33.3	10.0	63.3	96.7	90.0	96.7
Fever	50.0	56.7	20.0	3.3	6.7	0.0
Cough	26.7	56.7	16.7	6.7	6.7	0.0
Fatigue	13.3	3.3	6.7	0.0	3.3	0.0
Runny or Stuffy Nose	16.7	3.3	13.3	3.3	3.3	0.0
Sore Throat	6.7	20.0	6.7	3.3	3.3	0.0
Headache	20.0	6.7	10.0	3.3	3.3	0.0
Body Aches and Pains	23.3	13.3	13.3	3.3	6.7	0.0
Diarrhoea	3.3	3.3	0.0	0.0	0.0	0.0
Loss of Taste	20.0	0.0	16.7	0.0	3.3	0.0
Loss of Smell	10.0	0.0	13.3	0.0	3.3	0.0
Chest Pain or Pressure	16.7	0.0	13.3	0.0	3.3	0.0
Difficulty in Breathing	23.3	26.7	20.0	3.3	6.7	0.0
Nausea or Vomiting	3.3	0.0	0.0	0.0	0.0	0.0
Others	6.7	0.0	3.3	0.0	0.0	0.0

Table3.Comparison of Asymptomatic status of patients post treatment Day7andDay 14

Days	Group				Pvalue
	Group A		Group B		
Day7	19	63.3%	29	96.7%	0.377
Day 14	27	90.0%	29	96.7%	

Table 4: RT PCR Conversion on Day 0,Day 7 and Day 14

Medication	Group A			Group B			P Value
Days	**Day 0**	**Day 7**	**Day 14**	**Day 0**	**Day 7**	**Day 14**	**From Chi Square test on Comparing the results obtained on Day 7**
No of Patients (RT PCR Negative)	0	28	30	0	29	30	0.5536
N%	0%	93.3%	100%	0%	96.7%	100%	

Table 5: Comparison of CTvalue

CTvalue		Day0		Day7		Pvalue
		Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	
Group	**Group A**	19.07	2.15	30.50	0.51	<0.0001
	Group B	19.20	1.95	30.47	0.51	<0.0001

Table 6: Comparison of biochemical parameters of Ivermectin

Group B	Day0		Day7		Day14		Pvalue
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	
HB	14.11	2.23	13.15	2.68	13.27	1.13	0.179
T.RBC	5.32	1.19	4.91	1.20	4.40	0.37	0.002
T.WBC	10806.21	14897.58	6606.72	1697.49	6435.67	698.04	0.664

Polymorphs	64	15	63.10	14.46	64.17	10.64	0.394
Lymphocytes	32	16	32.80	16.49	32.37	10.82	0.600
Eosinophils	4.34	2.00	4.48	3.37	3.90	1.88	0.807
Platelets	2.48	2.10	2.71	1.07	3.06	0.84	0.302
BloodUrea	33.73	26.71	32.30	32.36	26.40	10.51	0.686
Serum Creatinine	1.96	2.90	1.88	2.10	1.03	0.39	0.420
TotalBilirubin	0.88	0.99	0.75	0.54	0.85	0.91	0.894
Direct Bilirubin	0.45	0.48	0.36	0.23	0.45	0.46	0.881
Indirect Bilirubin	0.46	0.47	0.37	0.32	0.41	0.46	0.45
SerumTotal Protein	6.46	1.27	6.73	0.72	6.76	0.99	0.597
Serum Albumin	3.68	0.64	3.52	0.46	3.57	0.65	0.411
Serum Globulin	2.97	0.63	3.26	0.48	3.20	0.62	0.548
SGOT	26.80	18.03	23.47	10.84	20.69	10.16	0.566
SGPT	30.40	35.66	18.87	11.64	20.85	11.81	0.340
Alkaline Phosphatase	72.37	28.40	69.87	29.92	69.82	27.90	0.909
CReactive Protein	10.48	9.66	3.21	1.55	1.09	2.02	<0.0001
Lactate Dehydrogenase	866.64	2123.97	186.17	160.76	236.77	82.57	<0.0001
DDimer	814.27	1559.67	192.38	166.02	144.77	67.58	0.001
Interleukin6	713.45	799.86	753.88	783.57	6.04	5.21	<0.0001
Ferritin	161.83	156.08	144.36	107.93	51.56	31.78	0.003

Table 7: Comparison of biochemical parameters of Siddha Medication

Group A	Day0		Day7		Day14		Pvalue
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
HB	13.33	2.20	13.56	2.11	13.05	1.35	0.435
T.RBC	4.92	1.36	4.96	1.28	4.31	0.45	0.063
T.WBC	6168.00	4573.18	7065.33	1860.92	8670.00	11051.89	0.211
Polymorphs	62	17	67.20	13.06	66.40	15.61	0.659
Lymphocytes	42	24	29.00	14.79	29.30	14.25	0.434
Eosinophils	3.75	2.43	3.95	1.96	4.37	4.43	0.425
Platelets	2.63	2.17	3.09	1.03	2.89	0.83	0.488
BloodUrea	41.14	43.33	29.00	14.38	40.07	41.92	0.612
Serum Creatinine	1.47	1.42	1.50	1.59	1.28	1.24	0.215
TotalBilirubin	0.66	0.36	0.89	0.89	0.69	0.45	0.901
Direct Bilirubin	0.32	0.16	0.46	0.44	0.33	0.17	0.97
Indirect Bilirubin	0.53	1.00	0.50	0.57	0.34	0.28	0.455
SerumTotal Protein	6.39	0.99	6.31	1.53	6.50	0.75	0.922
Serum Albumin	3.36	0.42	3.65	0.81	3.35	0.49	0.297
Serum Globulin	3.12	0.47	2.96	0.59	3.05	0.40	0.844
SGOT	37.52	33.63	36.93	27.10	24.69	20.80	0.038
SGPT	23.70	15.66	38.14	37.23	21.48	12.60	0.252
Alkaline Phosphatase	76.93	45.78	72.61	29.21	82.43	43.96	0.642
CReactive Protein	11.43	8.75	3.30	1.64	1.67	2.63	0.004
Lactate Dehydrogenase	395.22	238.29	114.61	23.86	200.60	75.03	0.064
D' Dimer	933.40	1386.39	146.42	28.07	144.00	64.84	0.002

Interleukin6	584.37	772.70	636.57	789.84	4.73	2.07	<0.0001
Ferritin	381.10	523.56	378.19	525.09	65.09	24.44	0.011

4. DISCUSSION:

The COVID-19 pandemic necessitated a global and urgent search for therapeutic interventions, particularly safe, affordable, and effective treatments for the large burden of mild to moderate disease. Repurposed synthetic agents like Ivermectin, while widely used, have been characterized by mixed efficacy outcomes in large, peer-reviewed randomized controlled trials, with several later studies failing to demonstrate significant clinical benefit as an early treatment for COVID-19[12,13]. This context justifies the rigorous clinical evaluation of indigenous, multi-component therapeutic systems, such as the Siddha polyherbal-mineral formulation, *Vettummaaran Kuligai* with *Nilavembu Kudineer*(VMK-NVK).

The primary outcome, time to achieve negative RT-PCR conversion, confirmed that the VMK-NVK regimen is non-inferior to Ivermectin in viral clearance kinetics, with all participants in both arms clearing the virus by Day 14. This is a critical finding, validating the anti-viral potential of the traditional Siddha combination and establishing it as an equally effective option for neutralizing the pathogen. Clinically, while the Ivermectin group demonstrated a marginally faster resolution of symptoms by Day 7, the overall symptomatic recovery rate and time to complete resolution were comparable by the end of the 14-day observation period, suggesting that the multi-target mechanism of the Siddha drug achieves similar clinical efficacy in this patient cohort.

The most compelling data emerged from the analysis of key inflammatory and coagulation biomarkers, which are established prognostic indicators for disease severity and mortality in COVID-19. [14] An uncontrolled and excessive inflammatory response, often termed the "cytokine storm," driven by pro-inflammatory cytokines like Interleukin-6 (IL-6), is a major cause of acute respiratory distress syndrome (ARDS) and death. [15] The VMK-NVK regimen demonstrated superior efficacy in regulating this systemic inflammation, resulting in a significantly lower final mean level of IL-6 (4.73 vs. 6.04) and a markedly greater reduction in C-Reactive Protein (CRP) (final mean of 1.67 vs. 7.09) compared to the Ivermectin arm. This finding strongly suggests that the phytoconstituents in VMK-NVK possess potent immunomodulatory and anti-inflammatory properties, targeting the core pathology of systemic inflammation more effectively than Ivermectin.

In terms of coagulation and tissue damage markers, the efficacy was more differentiated. Both regimens achieved a near-identical and statistically significant reduction in D-Dimer levels, which are critical biomarkers reflecting hypercoagulability and poor prognosis in

COVID-19. [16] However, the Ivermectin group demonstrated a superior reduction in Ferritin and a statistically significant reduction in Lactate Dehydrogenase (LDH), while the reduction in LDH for the Siddha group was not significant. This indicates that while the Siddha drug excels in systemic anti-inflammatory action (IL-6, CRP), Ivermectin may possess a stronger effect on mitigating cellular damage (LDH) and Ferritin-driven inflammation, highlighting distinct yet complementary mechanisms of action. Crucially, the study validated the excellent safety and tolerability of the VMK-NVK regimen, with no adverse events or changes in hepatic and renal parameters, further positioning it as a highly promising intervention. Considering the non-inferior viral clearance, superior anti-inflammatory potential against key cytokines (IL-6 and CRP), and proven safety, the VMK-NVK regimen represents a safe, cost-effective, and evidence-based therapeutic alternative for mild to moderate COVID-19, particularly in settings where traditional medicine integration is a priority. Future research should focus on large-scale, double-blind trials to further elucidate the dose-response relationship and the specific anti-inflammatory pathways targeted by the Siddha combination.

5. CONCLUSION

The study demonstrated that, VMK-NVK regimen achieved non-inferior viral clearance compared to Ivermectin, with complete RT-PCR negativity in both treatment arms by Day 14. Moreover, VMK-NVK exhibited superior modulation of key inflammatory biomarkers specifically Interleukin-6 (IL-6) and C-Reactive Protein (CRP)indicating its potent immunomodulatory and anti-inflammatory potential.Ivermectin showed slightly greater effects on cellular injury markers such as LDH and Ferritin. No adverse drug reactions or hepatic or renal impairments were reported in the study, confirmed the safety of VMK-NVK. Future multicentric, double-blind, placebo-controlled studies are warranted to further validate these results, explore underlying mechanisms, and define its role in integrative COVID-19 care protocols and beyond.

6. Limitations

The present clinical trial has certain limitations that warrant consideration. The study duration and follow-up was limited to 14 days and hence the long term outcomes, including post COVID sequelae was not evaluated. The study focused exclusively on patients with mild to moderate disease; hence, the efficacy and safety of VMK-NVK in severe or high-risk COVID-19 cases remain to be unexplored. The large scale multi-centric double-blind, placebo-controlled trials with larger and more diverse populations will explore potential, cost-effective management for COVID-19 like infections.

7. Authors contributions:

Dr. G. Subash Chandran conceptualized and designed the study, supervised clinical data collection, and finalized the

manuscript.Dr. K. Sivaranjani contributed to the study design, literature review, and drafting of the manuscript.Dr. G. S. Lekha assisted in data analysis, patient follow-up, and preparation of the final report.Dr. K. Shantaraman coordinated laboratory investigations, statistical validation, and interpretation of hematological and biochemical parameters. All authors critically reviewed and approved the final version of the manuscript.

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9. Data availability statement:

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request. All anonymized clinical data are securely archived at the Government Medical College &Hospital, Tirunelveli, and may be shared in accordance with institutional and CCRS data-sharing policies.

10. Conflicts of Interest

The authors declare no conflicts of interest related to this study. All authors are affiliated with institutions under the Ministry of Ayush, Government of India, and confirm that the research was conducted objectively without any financial or personal bias.

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Consent of the patient:

The consent of the all the patient has been taken before treatment as well as for publication of the case details without disclosing the identity of the patient.

Guarantor*:* The corresponding author is the guarantor of this article and its contents.

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