Journal of Ayurveda and Integrative Medicine 13 (2022) 100589

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Original Research Article

Safety and efficacy of a Siddha Medicine fixed regimen for the treatment of asymptomatic and mild COVID-19 patients

M. Kannan [a, *], P. Sathiyarajeswaran [a], D. Sasikumar [b], A. Geetha [a], M. Mohanapriya [a], N.P. Vinod [a], P. Manickam [c], K. Kanakavalli [d], P. Parthibhan [e], M. Pitchiah Kumar [f], R. Kannan [g], G. Sivaraman [h]

[a] Siddha Central Research Institute, CCRS, Chennai, India
[b] Govt. Siddha Medical College, Chennai, India
[c] ICMR-National Institute of Epidemiology, Chennai, India
[d] Central Council for Research in Siddha, Ministry of AYUSH, Chennai, India
[e] Department of Indian Medicine and Homeopathy, Government of Tamil Nadu, Chennai, India
[f] State Licensing Authority (Indian Medicine), Chennai, India
[g] IMPCOPS, Chennai, India
[h] Member, COVID-19 Taskforce Committee, Govt. of Tamil Nadu, Chennai, India

ARTICLE INFO

Article history:
Received 12 December 2021
Received in revised form
8 May 2022
Accepted 11 May 2022
Available online 23 May 2022

Keywords:
COVID-19
Siddha medicine
Standalone intervention
Kaba Sura Kudineer
Notchi Kudineer

ABSTRACT

Background: The Coronavirus disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a massive threat to public health worldwide. Siddha system of medicine is one of the traditional medicines of South India. The recommended formulations in Siddha Sasthric Medicines- Fixed Regimen (SSM-FiRe) are *Amukkura* tablets, *Kaba Sura Kudineer* (KSK) for asymptomatic COVID-19 positive (RT-PCR) patients, and *Athimathuram* tablets, *Adathodai Manappagu* syrup, *Thippili Rasayanam, Brahmananda Bairavam* tablet, and *Notchi Kudineer* for mild symptomatic patients. The core objective of the trial was to document the efficacy of SSM-FiRe in the prevention of asymptomatic and mild COVID-19 disease progression to the next level of severity, reduce the severity of symptoms and revert to RT-PCR Negative.

Methods: An exploratory, prospective, open-labeled, single-arm, non-randomized trial was designed as per GCP guidelines to assess the efficacy of SSM-FiRe. Sixty RT-PCR positive participants who were asymptomatic or with mild COVID-19 symptoms were recruited for the study at the Siddha COVID Care Centre, Vyasarpadi, Chennai from June to August 2020. Nasal and oropharyngeal swab tests were performed on the 0, 7th, and 14th days. All participants were treated with SSM – FiRe regimen. All the participants were also assessed based on Siddha *Yakkkaiyin Ilakkanam*, which included Clinical symptoms and vitals. Laboratory investigations such as Haemogram, Liver Function Test, Renal Function Test, HbA1C, Electrolytes, Inflammatory markers, Cardiac profile, Immunoglobulins, and anti-SARS-CoV-2 antibody tests were performed.

Results: 83% of COVID-19 patients turned RT-PCR negative on the 7th day and in most of the cases, symptoms were reduced within the first 5 days of admission. The RT-PCR cycle threshold (ct) value increased significantly (<0.001) after treatment and all the participants were RT-PCR negative, except one, who was positive even after 14 days. Anti-SARS-CoV-2 antibodies developed significantly (p-value – 0.006). LFT, RFT, CBC, Total proteins, and electrolytes continued to be in the normal range after treatment, indicating the safety of the intervention.

Conclusion: Asymptomatic and mild COVID-19 disease can be well managed by SSM – FiRe treatment, Further studies could be taken up to strengthen the findings.

* Corresponding author.
E-mail: siddhikanna@gmail.com
Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2022.100589

1. Introduction

Siddha system of medicine is one of the traditional systems of medicine prevalent in South India. The classical Siddha system mentions 4448 diseases that are developed by the derangement of three humor (Vali, *Azhal, and Aiyam*). These diseases are diagnosed by clinical examination and eight-fold examination (*Envagai thervu*) which includes the tools such as *Naa* (Tongue), *Niram* (Colour), *Mozhi* (Speech), *Vizhi* (Eyes), Naadi (Pulse diagnosis) *Sparisam* (Sensation), *Malam* (Stool), *Moothiram* (Urine), etc. and treated with Siddha Sasthric Medicines (SSM) [1].

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered Coronavirus termed SARS-CoV-2. It is a massive threat to public health worldwide. Current estimates suggest that the novel coronavirus is both highly contagious and it is more lethal than seasonal influenza (estimated CFR-2.79%) [2].

WHO stated that the cases of COVID-19 all over the world, as of 01 October 2021 there were more than 233, 503, 524 confirmed cases and 4,777,503 deaths due to this pandemic. In India more than 33, 766,707 confirmed COVID-19 cases and deaths 4,48,339 as of 01.10.2021 [3]. It all started with an unknown cause detected in Wuhan, China, which was first reported to the WHO Country Office in China on 31st December 2019. The outbreak was declared as a Public Health Emergency of International Concern on 30th January 2020 [4]. In Tamil Nadu 2,665, 386 confirmed cases and 35,603 deaths were recorded up to Oct. 02, 2021 [5]. The SARS-CoV-2 virus is airborne and spreads rapidly through cough and sneezing.

Over the past year, several vaccines were developed and rolled out but as of date, there are no drugs that can prevent or treat the disease. The existing antivirals and antimalarials in the allopathy system such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine, hydroxychloroquine, and interferons have been repurposed in the recent past due to its proven inhibitory effects against the SARS-CoV-2 [6]. In prior studies, the drug Dexamethasone was found to offer 28-day lower mortality in hospitalized, critically ill COVID-19 patients [7]. Hence, there is a dire need for interventions that can prevent COVID-19 disease progression and fatalities.

The world is now interested to reinstate the ancient practice among the public. Therefore, it is the need of the hour to scientifically validate the herbs and herbal formulations against SARS-CoV-2 [8]. Although several drug trials are ongoing all over the world, there is scope for Traditional Medicine to be tested against COVID-19. In classical textbooks of Siddha medicine, epidemics and pandemics termed as *Uzhi Noi* or *Kothari Noi* or collectively *Kollai Noigal* have been explained and their possible treatment [9]. This study is investigating the efficacy of a Siddha Medicine regimen in COVID-19 management and recovery from the infection.

Generic anti-virals of the allopathic system are repurposed in every pandemic. This COVID-19 pandemic has >10−20 repurposed drugs from Siddha medicine, which are formulations that are traditionally used in the treatment of cold, cough, fever, malaise, breathlessness, and fever with respiratory illness, sore throat, running nose, etc. [10]. The individual herbal formulations of *Aadathodai Manappagu* (AM) [11], *Notchi Kudineer* (NK) inhibit the SARS-CoV-2 virus in *in-vitro* studies. *In-silico* studies have indicated that phytoconstituents in *Kaba Sura Kudineer* (KSK) [12], *Notchi Kudineer* (NK) [13], *Adathodai Kudineer* (AK) [14], *Thontha Sura Kudineer* (TSK) [12], target the spike protein of SARS-CoV-2 virus, thereby making them potential drugs. KSK, a Siddha medicine with 15 herbs, showed a high binding affinity against SARS-CoV-2 spike protein. Chrysoeriol and Luteolin from KSK have shown the highest dock score values of above 11.00 [15]. P4 is the new proactive approach to preventing diseases which has predictive, preventive, personalized, and participatory [16]. Siddha medical tradition has a trihumoural basis in which each individual is characterized into *Vali (Vatham), Azhal (Pitham)*, and *Aiyam (Kabam)* and there is a predictive approach in diagnosis. Further, there is always an inclusiveness and participatory approach towards the diet and lifestyle modifications based on each condition. Always Siddha advocates the prevention of the diseases. Its emphasis the personalized approaches in treatment and diagnosis based on individual constitution and stages of the disease.

During the start of the pandemic (March 2020), when there were no drugs or vaccines, the Tamil Nadu Government in collaboration with the Ministry of AYUSH, Government of India, setup up Siddha COVID Care Centre (SCCC) across Tamil Nadu. This study was undertaken in one such COVID-19 care center (single-center) using the standard regimen of Siddha Sasthric Medicine in asymptomatic and mild cases following the Ayush Good Clinical Practice [17]. All the above Siddha formulations have been officially recommended by the Tamil Nadu Government, in earlier viral epidemics like Dengue, Swine flu, and Chikungunya [18]. The recommended formulations in Siddha are *Nila Vembu Kudineer (NVK), Kaba Sura Kudineer (KSK), Visha Sura Kudineer (VSK)*, and *Adathodai Manappagu* syrup [19].

Clinical features of COVID-19 include fever, cough, fatigue, shortness of breath, expectoration, myalgia, rhinorrhea, sore throat, and diarrhea. A few people report loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms. Older people and immune-compromised patients, in particular, may present symptoms such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, and absence of fever [20], and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The traditional drug regimen that helps to reduce the onset of COVID-19 and prevent the disease progression is the need of the hour.

In order to support the Health and Family Welfare Department, Government of Tamil Nadu, a proposal has been set up to analyze the effect of SSM-FiRe, a Siddha drug regimen to combat COVID-19. This has been jointly proposed and convened by the Directorate of Indian Medicine and Homoeopathy, the office of the State Licensing Authority (Indian Medicine), Chennai, and the Central Council for Research in Siddha, Ministry of AYUSH, Govt. of India. The objective was to determine the efficacy of SSM-FiRe in preventing the COVID-19 disease progression of asymptomatic, and mild stage COVID-19 patients at the study site Siddha COVID Care Centre (SCCC), Vyasarapadi, Chennai.

2. Methods

2.1. Study design

The study was an interventional prospective, open-label, single-arm, non-randomized trial, Phase II (Exploratory) study, conducted over three months from June to August 2020. This study intended to explore the efficacy and safety of SSM-FiRe for asymptomatic (COVID-19 positive with no symptoms) and Mild symptomatic (COVID-19 positive with mild symptoms) [20] patients. The study was approved by the Institutional Ethics Committee (IEC) of Government Siddha Medical College, Arumbakkam, Chennai (**GSMC-CH-3402/ME-2/044/2020**). The Trial has been registered in the Clinical Trial Registry of India, prospectively (CTRI No: **CTRI/2020/07/026471**). All the interventional drugs were sponsored and supplied by the Indian Medical Practitioners Co-operative Society (IMPCOPS), 34−37, Kalki Krishnamurthy Salai, Thiruvanmiyur, Chennai-600041 (GMP Certified Manufacturer).

2.2. Clinical assessment

History of illness, the probable source of exposure to SARS-CoV-2 infection, the demographical profile, vital signs, comorbidities, signs, and symptoms as per Siddha, and modern aspects were assessed. Vitals including SpO_2, pulse rate (PR), body temperature were obtained daily for all the participants. The effect of the interventional drug on immunity was assessed through the investigation of immune markers. The ADR/AE for the interventional Drug SSM-FiRe was documented.

Assessment of the body constitution was done as per Siddha classics, for all the participants based on the standardized and validated Siddha *YI* Tool-www.siddhayitool.com, as an Immune assessment. It comprises a questionnaire to assess the body functions, mental, and physical profiles [21] was obtained. The Siddha YI tool assessment was done on day 1 only. Siddha Fundamental Factors like *Uyir Thathukkal* Assessment and *Udal Thathukkal* Assessment were taken on the 0th day, 7th day, and 14th day.

2.3. Laboratory investigations

Nasal and oropharyngeal swab (RT-PCR, Ct Value), Serology (Anti-SARS-CoV-2 antibody) were investigated before treatment (0th or 01st day) and after treatment (07th or 14th day as per the RT-PCR swab test result). HbA1C was done for the assessment of Glycaemic control, If the person has Diabetes mellitus (DM) comorbidity existed. All other investigations were done before the treatment (0th Day) and after the treatment with the SSM-FiRe (7th or 14th Day) based on the RT-PCR Negative report. If the patient becomes RT-PCR Negative on the 7th Day investigation, the 14th day investigation was withdrawn. List of investigations: Haemogram Hb%, total leucocyte count and differential WBC (neutrophils, lymphocytes, eosinophils, monocytes and basophils), RBC count, platelet count, Liver Function Test (Bilirubin, ALT, AST, alkaline phosphatase, GGT, Total Protein, Albumin, Globulin), Renal Function Test (BUN, Creatinine), Blood sugar (HbA1C), Electrolytes (Sodium, Potassium, Chloride, Bicarbonate), Inflammatory profile (CRP), Cardiac profile (LDH, CPK, D Dimer), Immunoglobulins [Th1 (TNF-Alfa, IFN-gamma, IL2), Th2 (IL6, IL10)].

2.4. Inclusion criteria

All patients were screened through questions like the date of sample collected for RT-PCR and positive result and the date of onset of symptoms was noted. Patients with recently (within 2 days) RT-PCR positive or symptoms onset patients were enrolled in the study. The asymptomatic and mild category of COVID-19 demarcated in the Clinical Management Protocol by the Ministry of Health and Family Welfare, Govt. of India were followed for the study [22]. Adult Male/Female age $\geq$18 years, who can provide written informed consent, COVID-19 Positive as determined by RT-PCR, with no clinical signs or with mild symptoms – malaise/fatigue, cough, muscle pain, anosmia, ageusia, headache, joint pain, sore throat, loss of appetite, diarrhoea, fever, sleeplessness, shortness of breath, indigestion, throat pain, heartburn, nausea, shivering, abdominal pain, vomiting, nausea, sneezing, constipation were enrolled in the study.

2.5. Exclusion criteria

RT-PCR negative patients on the 0th day, were excluded from the study. Pregnant and lactating females; COVID-19 Positive with severe symptoms – respiratory distress (>24 breath per minute), Oxygen saturation <90% at rest, known cases of uncontrolled Diabetes (>9% HbA1c); subjects having any medical or surgical condition that would require immediate medical or surgical intervention at the time of screening; subjects having immune-compromised conditions like HIV, Hepatitis, Tuberculosis, Cancer, etc.; participants on steroid treatment and or any kind of immunosuppressive therapy; participants enrolled in any other clinical study or having participated in any other study 1 month prior to screening in the present study; participants having a past history of allergy to Siddha medicine; participants with <7 g/dL Hb were excluded.

2.6. Sample size

As an exploratory study, 60 asymptomatic and mild COVID-19 positive were recruited in the study to assess the efficacy of the drugs.

2.7. Ethical considerations

During the screening visits, voluntary written informed consent was obtained for the subject's participation in the study. Informed Consent Form (ICF) and Participant Information Sheet (PIS) was prepared in the regional language (Tamil) and explained to the subject/subject's Legal Authorised Representative (LAR). The PIS explained the objectives of the study, study procedure, responsibilities, possible risks, and benefits of participation in the study. They were given enough time/option to ask questions to fully understand the study. The care at the Siddha COVID Care Centre, medicines, and the clinical and laboratory assessments was free of charge for the participants.

3. Treatment

Asymptomatic and mild category patients were treated with medicines as listed (Table 1).

4. Results

4.1. Outcome measure

The outcome was assessed based on the RT-PCR report and assessment of clinical signs and symptoms. A positive outcome was considered if Ct value of RT-PCR of $\geq$35 or negative report or if the patient does not have any symptoms. Also, the assessment of Siddha parameters based on the three humours (*Vali, Azhal, and Aiyam*) was found to be normal from the date of confirmation was taken as outcome measures for the treatment and discharge of the participant. After discharge, the participants were advised to stay in quarantine for up to 17 (14 + 3) days in total from the first day of RT-PCR positive. Participants were advised to take as per the Aarokyam Kit medicines (*Amukkara Chooranam Mathirai* and *Nellikai Ilagam*) as follow-up medicines by the Govt. of Tamil Nadu [26].

4.2. Baseline data

Totally 196 participants were approached for the trial; 110 patients were screened and 43 excluded based on the initial RT-PCR swab test; 5 dropped out and 1 was not willing for investigations (Fig. 1). 1 female participant suspecting pregnancy was also excluded from the trial. 60 participated in the trial, in which 13 were asymptomatic and 47 were mild symptomatic.

Among the 60 participants, 28 were males and 32 were females. Most of those who participated were Hindus (95%), 65% of them were not aware of the source of infection. 33.3% of participants were in the age group of 41–50, 18–30, and 31–40 were 25% each, and the remaining (16.7%) were between the age group of 51–60 (Table 2).

Table 1
Siddha Sasthric Medicines in Fixed Regimen (SSM-FiRe) for COVID-19.

S. No	Name of the Medicine	Oral Dose	Reference
Asymptomatic category			
1.	Kaba Sura Kudineer [11,23]	60 ml twice daily, Before food	Siddha Vaithiya Thirattu, 1998, P293
2.	T. Amukkara Chooranam [23,24]	2 tab. twice daily, After food	Siddha Vaithiya Thirattu, 1998, P213
Mild symptomatic category			
3.	T. Athi Mathuram 500 mg [10]	2 tab. twice daily, After food	Siddha Formulary of India Part II, 2011, P150,151
4.	T. Brahmananda Bairavam 100 mg [23,24]	2 tab. twice daily, After food	Siddha Vaithiya Thirattu, 1998, P34
5.	Adathodai Manappagu [23]	10 ml, twice daily, After food	Siddha Vaithiya Thirattu, 1998, P259
6.	Thippili Rasayanam (23) [26],	5 gm twice daily, After food	Siddha Vaithiya Thirattu, 1998, P235
7.	Notchi Kudineer [23,25]	60 ml twice daily, before food	Siddha Vaithiya Thirattu, 1998, P294

Duration: 7–14 Days as per the outcome specification.

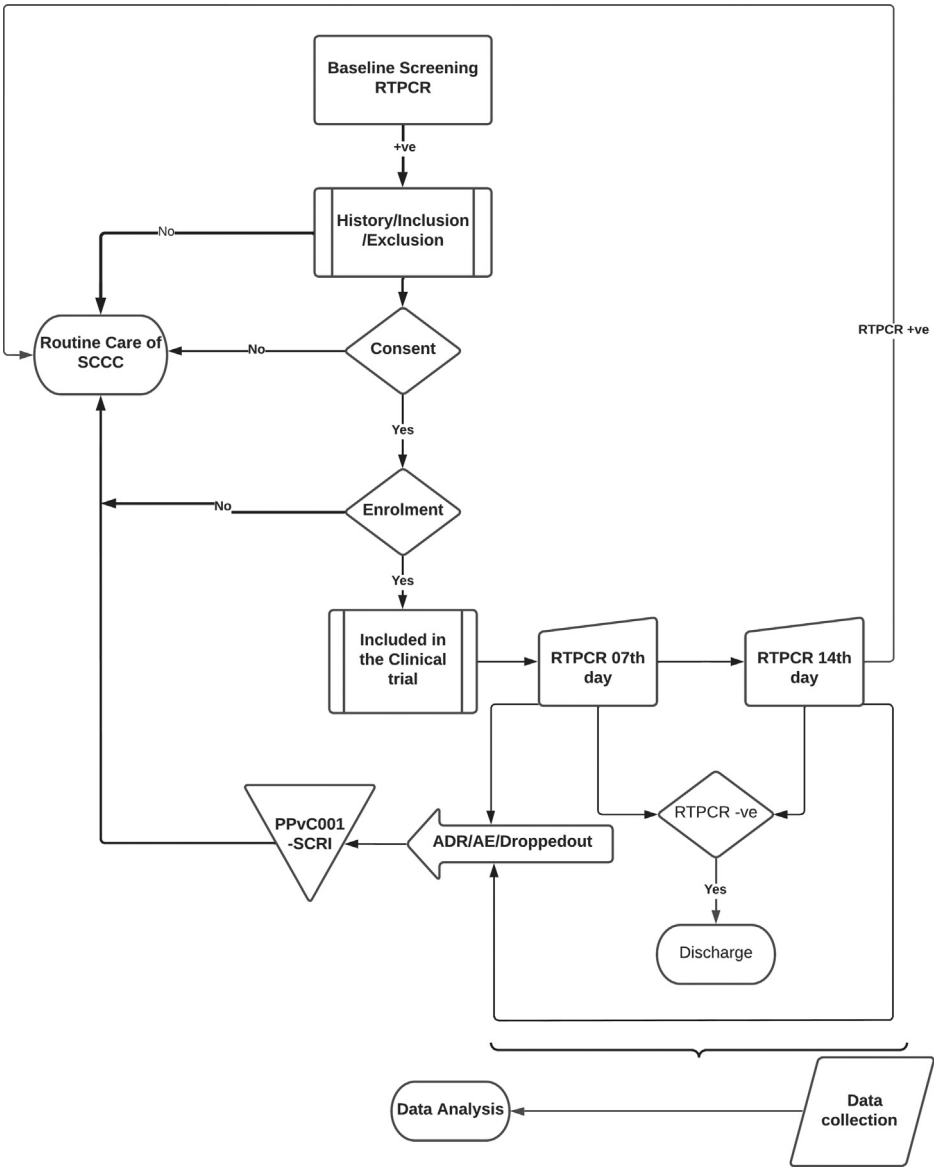

Fig. 1. Flowchart.

4.3. Symptom details

At the baseline 16.16% of participants had malaise/fatigue, 13.54% had a cough, 12.66% had anosmia, 10.92% had ageusia, 10.04% had muscle pain 5.46% had joint pain, 4.37% had a sore throat, 3.49% had a loss of appetite, 3.28% had diarrhoea, 9.6% had a headache, and only 2.18% had a fever. Sleeplessness, shortness of breath, indigestion was seen in less than 2% and some of the

Table 2
Socio-demographic and economic details of the trial participants.

Characteristics	Frequency	Percent
Age Group (years)		
18–30	15	25.0
31–40	15	25.0
41–50	20	33.3
51+	10	16.7
Male gender	32	53.3
Married	46	76.7
Completed schooling	18	30.0
Completed degree	35	58.3
Occupation		
Employed in desk work	9	15.0
Employed in physical labor	13	21.7
Fieldwork	15	25.0
Homemaker	20	33.3
Student	3	5.0
Above poverty line (APL)	41	68.3
Urban resident	53	88.3
Hindu religion	57	95.0
Primary contact of confirmed COVID-19	21	35.0

participants had throat pain, heartburn, nausea, shivering, sneezing, abdominal pain, vomiting, wheezing, and constipation were seen in less than 1%.

During the treatment period, the majority of the symptoms were reduced within 5 days, almost all the symptoms were reduced within 7 days and 1.7% of the patient had a cough, ageusia, and anosmia.

4.4. RT-PCR swab test

Out of 60 participants, 50 became RT-PCR negative on the 07th day, 2 on the 10th day, 7 on the 14th day and 01 participant did not turn negative even after the 14th day of treatment.

4.5. Assessment of body constitution

Among the 60 participants 41 *Azhal* constitutions, 5 *Vali* constitution, and 14 *Aiyam* constitutions were documented based on the responses given by the participants (Fig. 2).

4.6. ADR/AE

There were no Adverse Drug Reactions or Adverse events among the 60 participants.

4.7. Blood group

The study shows that 23 of 60 were O group, 32 were under A, B, and AB; and 5 were not tested.

4.8. Liver Function Test

The levels of parameters such as SGOT had some mild abnormality in post treatment which shows liver damage persistent due to COVID-19 which is associated with an increased incidence of liver injury [26–28] (Table 3).

4.9. Renal Function Test

BUN, Creatinine levels were normal in pre and post-treatment. 25% abnormality of Creatinine kinase in before treatment and reduced to 11.67%. Albumin and A/G Ratio normal in pre and post-treatment whereas globulin abnormality reduced from 23.33% to 16.67%.

Laboratory findings show some abnormality in LDH, D-Dimer, and CRP both before and after treatment.

There was no significant reduction in LDH. Before treatment LDH value was 425.53 ± 143.4 and after treatment, it increased escalated to 480.36 ± 148.4.

The D-Dimer value before treatment was 1003.63 ± 2270.69 and after treatment, it was 867.13 ± 1962.92. Electrolytes were normal and well maintained (Na, K+, Bicarbonate, and Cl value).

There was no significant difference in HbA1c levels before and after treatment as it was well maintained between 6.56% and 6.51%. There was no change in the platelet count in pre and post-treatment (Table 3).

4.10. Immunity markers

Anti-SARS-CoV-2 value significantly showed improvement towards normality and patients turning RT-PCR negative increased

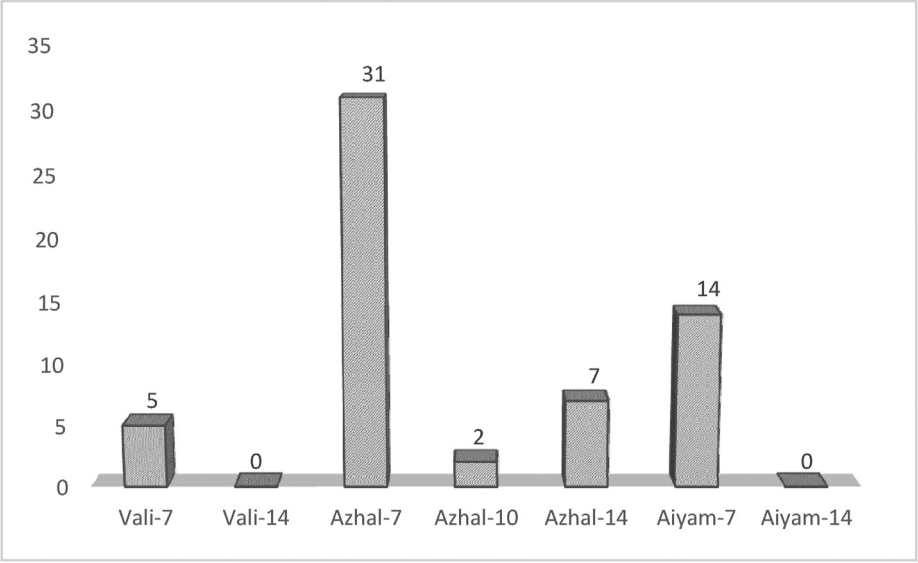

Fig. 2. Explains the Yakkai Ilakkanam vs Length of Stay.

Table 3
Laboratory findings.

Investigation	Normal Value	Pre treatment (Mean ± SD)	Post treatment (Mean ± SD)
LDH	180–360 U/L	425.53 ± 143.04	480.36 ± 148.4
CRP	≤6 Mg/L	7.2 ± 12.52	10.52 ± 22.74
D-Dimer	(Neg <500. Positive >500) ng/mL	1003.63 ± 2270.69	867.13 ± 1962.92
IL_6	0–4.4 pg/mL	39.27 ± 188.66	74.16 ± 217.18
HBA1C	4.0–5.6%	6.56 ± 1.83	6.51 ± 1.79
EAG	70–126 mg/dL	141.67 ± 52.59	140.24 ± 51.45
ANTI-SARS-CoV-2_AB	Non-R: < 1.0 | React: >/ = 1.0	1.09 ± 2.31	7.02 ± 17.48
TNF [29]	0–22 pg/mL	40.89 ± 227.59	3.7 ± 13.84
IL10	0–5 pg/mL	0.62 ± 2.44	0.78 ± 5.43
IFN	0–5.5 pg/mL	12.97 ± 98.35	6.06 ± 44.27
IL2	0–12 pg/mL	0.01	0.02 ± 0.03

during the stay period. There were no marked changes in IL2, IL10, TNF α, IFN ɣ, but increased IL6 levels in pre and post-treatment (Table 3).

5. Discussion

We did an exploratory open trial of recommended formulations from the Siddha system of medicine for asymptomatic COVID-19 confirmed individuals in terms of prevention of the clinical progression of asymptomatic/mild to the next level. We documented that none of the study participants progressed to the severe stage, and no mortality was reported. In terms of safety, except for mild elevated SGOT, no other alterations in the hepatic or renal parameters were observed.

The male preponderance has been explained in several previous studies as due to the high expression of ACE2 protein in Asian males which facilitates a pathogenic environment to the Corona infection [30] and male patients have higher mortality. In the public data set, the number of men who died from COVID-19 is more than that of women at a COVID Care center in Chennai, Tamil Nadu, India [31]. Married couples were more prone to infection (76.7%) as there is a human-to-human transmission in COVID-19 [32]. Young adults and middle-aged (31–50 years) were more prone to infection due to social activities. They were the breadwinners of their family and there was a need to go out for their jobs, while the older age group between 51 and 60 were staying home. The study results showed that only 3 were students among the 60 participants. This supports the positive reinforcement on lockdown due to COVID-19 pandemic in reducing the risk of infection. Moreover, a Chinese cross-sectional study on assessment of knowledge, attitude, and practice towards COVID-19 infection showed a significant difference among various age groups, genders, educational qualifications, and residence areas [33].

The most presented symptoms were malaise, cough, anosmia, muscle pain, headache, and sore throat [34]. Though the common clinical feature includes fever, only 5 among the 60 cases had fever on Day 1 which gradually reduced at Day 6 indicating that most of the cases were asymptomatic. A maximum of 4 cases had diarrhea on Days 4 and 5 and the other gastrointestinal symptoms such as nausea, vomiting, heartburn, and abdominal pain were not seen. It has been stated in previously published reports that the recovery started in the second or third week of the treatment period only. But this study documents that the recovery period and symptom reduction were started within day-7 (1 week). This early recovery period in Siddha management confirms the drug's efficacy [34].

RT-PCR cycle threshold (Ct) values as a semiquantitative measure of SARS-CoV-2 viral load and this test identifies the level of SARS-CoV-2 RNA in the Upper Respiratory Tract. The Ct value of before treatment shows (Mean ± SD) (21.39 ± 4.73), and after treatment was (34.97 ± 0.26). Thus, the Ct value of the RT-PCR test shows statistically significant value ($P < 0.001$) [28].

As per the Siddha classic [35], the constitution *Aiyam* has strong immunity, and the *Azhal* constitution has moderate immunity when compared with the *Vali* constitution with poor immunity [36]. The increased laboratory values indicate inflammation despite their improvement, subtle aspects of Siddha conveys that most of the subjects were of *Azhal Udal* and their length of stay was Day-7 and few cases at Day 14. The above results were indicating the same as described by the Siddha literature captured by the Siddha YI tool. According to the Siddha concept, *Azhal/Pitha Udal* has the *Azhal* predominant trihumoral make-up with a preponderance of fire component and therefore provoke the underlying inflammations [36]. Pathophysiologically, *Kaba suram* is concerned with aggravated *Kaba thodam (Thannilai Valarchi)* facilitating a favourable environment for any respiratory infection in regions of *Kabam* [37]. It is a noteworthy finding that this study involved more subjects with predominant *Azhal* Humour, which could be the probable cause of minimal cases with fever (*Amam*, the cause of fever is due to *Aiyam/Kabam*) and lesser respiratory symptoms such as shortness of breath, wheezing and progression of illness to COVID pneumonia despite the presence of elderly and cases with comorbidities. Although having the *Vali* constitution, the recovery rate from COVID-19 was faster than expected in the Siddha YI tool and one person of *Azhal* body constitution did not turn RT-PCR negative even after 14 days (Fig. 2).

The Siddha medicines probably have a similar anti-inflammatory action to the repurposed conventional drugs used in the pandemic and comparatively cost-effective treatment which needs to be explored in the future. Previously published works indicate that the ingredients of Kaba sura kudineer, Adhathodai manapaagu, Amukkara Chooranam Mathirai, Bramanandha Bairavam Mathirai, and Notchi kudineer are having Anti-viral, Anti-inflammatory, Anti-asthmatic, anti-diarrheal, and analgesic activities [13]. The molecular target action of the anti-inflammatory action of *Kaba Sura Kudineer* revealed the suppression of LPS induced pro-inflammatory cytokines TNF-α, IL-6, and PGE2 levels that owe to the present treatment outcomes of the study [39]. The arrival of effective vaccines has offered a ray of hope to the Governments, scientific communities, and the public throughout the globe. Even then effective pharmacotherapy is still lacking and Immunotherapies are the most expensive. The limited effectiveness of a few of the recommended treatments for COVID-19 including hydroxychloroquine, and remdesivir and the controversial role of corticosteroids in mild disease of non-oxygen requiring COVID-19 patients are the main reason for research undertaken by AYUSH

practitioners [40]. The present study highlights the clinical efficacy of herbo-mineral Siddha medicines in reducing viral load.

Significant improvement towards normalcy of Anti-SARS-CoV-2 value and increased turning of RT-PCR negative during the stay period shows the effect of SSM FiRe interventional package. The increased IL6 levels in pre and post-treatment show that IL6 plays a major role in this SARS-CoV-2 infection [41,42]. IL-6 has been identified to play a key role in the stimulation of cytokine storms and the progression of COVID-19 causing alveolar damage and extrapulmonary injury [41] The published literature relates the association of increased IL-6 with progression to severe stage of illness, and an elevated serum biomarkers CRP, D-dimer associated with a poor outcome in COVID-19 [43,44]. Even though the drug regimen is not observed to inhibit IL6 levels, still it has proven its efficacy towards the reduction in disease progression to severe stage. This warrants the molecular target action of these drug regimens and needs to be explored in further research.

In our present study, no significant changes were observed in IL2, IL10, TNF α, IFN γ and there was no need for intensive care admission of the enrolled cases. Off late, a monoclonal antibody that blocks Interleukin 6 (IL-6) signaling, comprises a remedial option against COVID-19 and their immunosuppressive effect might be valuable in patients with COVID-19 by controlling inflammation and promoting disease tolerance. But this is an expensive treatment option [45] and it is not affordable by all [44].

In terms of safety, elevated levels of SGOT indicate mild hepatocellular damage. However, none of the other renal and hepatic parameters, at the pre and post levels show any abnormalities and did not indicate hepatorenal toxicity. Similarly, though there was an increased LDH [46], D-Dimer [47–51], CRP at both pre and post-treatment, clinically most of the cases turned RT-PCR negative on the 7th day ($P < 0.001$), and almost in all the cases, marked reduction in symptom score was observed within first 5 days of admission. Even though there was a tendency towards normality in D-Dimer, it was not significant. However, a sufficient period of follow-up of the participants would provide a reduction in these inflammatory biomarkers. This would be of additional value for this study.

There is no significant difference in HbA1c levels pre and post treatment as it was well maintained between 6.56% and 6.51%. There was no change in the platelet count in pre and post-treatment, indicating that COVID-19 viral infection may not affect the platelets in the asymptomatic and mild COVID-19 patients.

5.1. Limitation

The study is an exploratory phase II, prospective, standalone treatment research. It is an open-labelled, single-arm, non-randomized trial with minimal sample size. Hence, the study has its own limitation and further controlled studies are required. The participants were recruited to the study from the SCCC, based on their willingness. Hence, selection bias may also be there. The study was performed at the early stage of the pandemic, and lack of evidence in the management of the disease, mostly everyone used their best available options for treatment.

6. Conclusion

We documented efficacy of the SSM-FiRe regimen in mild and asymptomatic COVID-19 based on clinical, virological outcomes, Siddha *Yakkkaiyin Ilakkanam*. There were no referrals to intensive care units. The regimen was found to be safe since there were no reported adverse events or no derangement in biochemical parameters.

7. Recommendation

We recommend further controlled studies and endorses the use of SSM-FiRe as a public health measure for the management of COVID-19.

Source of funding

The research is funded by the Central Council for Research in Siddha, Ministry of Ayush, Govt. of India. The funding body had no role in the design of the study and collection, analysis, and interpretation of data, and in writing the manuscript.

CRediT statements

Kannan: Conceptualization, Methodology, Validation, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization. **Sathiyarajeswaran:** Conceptualization, Methodology, Project administration. **Sasikumar:** Resources. **Geetha and Mohanapriya:** Investigation, Writing - Original Draft, Data Curation, **Vinod:** Formal analysis. **Manickam:** Writing - Review & Editing, Visualization, Supervision, **K. Kanakavalli and Parthibhan:** Project administration, **Pitchiah Kumar, Kannan, and Sivaraman:** Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgment

We submit our sincere thanks to the Ministry of Ayush, Govt. of India, and DG, CCRS. We submit our special thanks to Dr. Bhushan Patwardhan, Publication Management Unit, Ministry of Ayush, Govt. of India, and Dr. Padma Venkat, Publication Management Unit, Ministry of Ayush, Govt. of India.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2022.100589.

References

[1] Shanmugavelu M, Natarajan K, Anandan Anaivaari R. Principles of diagnosis in Siddha. 1st ed. Chennai: Department of Indian Medicine & Homeopathy; 2009. p. 406. 306.
[2] Oke J, Heneghan C. Global covid-19 case fatality rates-CEBM. URL, https.www.Cebm.Netcovid-19global-Covid-19-Case-Fatal-Rates. [Accessed 29 March 2020].
[3] WHO coronavirus disease (COVID-19) dashboard data [Internet]. World Health Organization. World Health Organization; 2021. 8:02 pm. Available from: https://covid19.who.int.
[4] WHO. Pneumonia of unknown cause — China [Internet]. WHO [cited 2021 Jul 28]. Available from: http://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/.
[5] GitHub - CSSEGISandData/COVID-19: novel coronavirus (COVID-19) cases, provided by JHU CSSE [Internet]. GitHub [cited 2021 Jul 28]. Available from: https://github.com/CSSEGISandData/COVID-19.
[6] Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. Pharmacol Rep 2020:1–30.
[7] Ahmed WS, Anand A, Stanbrook MB. Dexamethasone in hospitalized patients with COVID-19 preliminary report: discussions from the respirology and sleep Twitter journal club @respandsleepjc (#rsjc). Can J Respir Crit Care Sleep Med 2021 Jul 4;5(4):270–2.
[8] Khanna K, Kohli SK, Kaur R, Bhardwaj A, Bhardwaj V, Ohri P, et al. Herbal immune-boosters: substantial warriors of pandemic covid-19 battle. Phytomedicine 2021 May;85:153361.
[9] Noi Illa Neri. Kilpauk, Chennai: Indian Medical College; 1951. p. 321–9.
[10] Siddha formulary of India Part II. 1st ed. Ministry of AYUSH, Govt of India; 2011. p. 150–1.

[11] Ministry of AYUSH. NAM, D.O.No.S.16030/18/2019. Govt. of India; 2020.
[12] Pitchiah Kumar M, Sundaram KM, Ramasamy MS. Coronavirus spike (S) glycoprotein (2019-ncov) targeted siddha medicines kabasura kudineer and thonthasura kudineer—in silico evidence for corona viral drug. AJPRHC 2019;11:1—9.
[13] Ragaroobine A, Ragavanee A, Adaikalam SJM, Kabilan N, Seshayyan S. An exploratory review of PHARMACOLOGICAL activities of notchi kudineer-a siddha herbal decoction used in covid-19. Int J Ayurveda Pharma Res 2021: 59—66.
[14] Gnanaraj Johnson C, Krishnasamy R, Sekar P, Murugan R, Ponnappan S, Ramasamy M. Phytochemical screening of adathodai kudineer a siddha concoction and evaluation of binding affinity of its constituents with SARS-CoV-2 spike protein and ACE2 receptor spike protein complex through molecular docking in-silico approach. 2020.
[15] Gangarapu K, KM K, Ms S. In silico computational screening of kabasura kudineer-official siddha formulation and JACOM-novel herbal coded formulation against SARS-CoV-2 spike protein. 2020.
[16] Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. N Biotech 2012;29(6):613—24.
[17] Good clinical practice guidelines for ayurveda, siddha and unani medicine (GCP-ASU). Ministry of AYUSH, Govt of India; 1—104 p.
[18] The Wire. Tamil Nadu Government distributes herbal concoction to "cure" dengue. The Wire.-19 Oct 2017.
[19] Sabarianandh JV, Bernaitis L, Manimekalai K. COVID-19 in siddha medicine: a review. 2020.
[20] Ministry of Health and Family Welfare. Clinical management protocol, version 3. Govt. of India; 2020. p. 3—4.
[21] Siddha-YIABC [Internet] [cited 2021 Jul 28]. Available from: https://www.siddhayitool.com/.
[22] Directorate General of Health Services EMR Division. Final guidance on mangaement of covid cases, version2 [Internet]. Ministry of Health & Family Welfare, Govt. of India. Available from: https://www.mohfw.gov.in/pdf/FinalGuidanceonMangaementofCovidcasesversion2.pdf.
[23] Siddha Vaithiya Thirattu 1998:293—4. 213, 34,259,235.
[24] Jain J, Narayanan V, Chaturvedi S, Pai S, Sunil S. In vivo evaluation of withania somnifera—based Indian traditional formulation (Amukkara choornam), against chikungunya virus—induced morbidity and arthralgia. J Evid-Based Integr Med. 2018;23. 2156587218757661.
[25] Lalithambigai G, Sakthiganapthi M, Prakash Yoganandam G, Gopal V. Pharmacognostical Standardization, GC-MS analysis and in vitro screening of AN OFFICIAL SIDDHA FORMULATION- "NOCHI KUDINEER. Int J Exp Pharmacol 2017;7(2):43—6.
[26] AAROKYAM. G.O.(Ms). No.201 [Internet]. Health and Family Welfare (IM1-1) Department, Govt. of Tamil Nadu; 2020 [cited 2021 Jul 28]. Available from: https://stopcorona.tn.gov.in/wp-content/uploads/2020/03/AAROKYAM.pdf.
[27] Ali N, Hossain K. Liver injury in severe COVID-19 infection: current insights and challenges. Expet Rev Gastroenterol Hepatol 2020 Oct 2;14(10):879—84.
[28] Li Y, Xiao S-Y. Hepatic involvement in COVID-19 patients: pathology, pathogenesis, and clinical implications. J Med Virol 2020;92(9):1491—4.
[29] Kullar R, Patel AP, Saab S. Hepatic injury in patients with COVID-19. J Clin Gastroenterol 2020 Nov;54(10):841—9.
[30] Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020 Sep 1;202(5):756—9.
[31] GOI . Government of India. COVID-19 statewise status as on 13th July 2020. New Delhi: Ministry of Health and Family Welfare, (MoHFW); 2020. https://www.mohfw.gov.in/.
[32] Liu X, Zhang S. COVID-19: face masks and human-to-human transmission. Influenza Other Respir Viruses 2020 Jul;14(4):472—3.
[33] Zhong B-L, Luo W, Li H-M, Zhang Q-Q, Liu X-G, Li W-T, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int J Biol Sci 2020;16(10):1745—52.
[34] Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020 Apr;87(4):281—6.
[35] Muthiah K, Ganesan K, Ponnaiah M, Parameswaran S. Concepts of body constitution in traditional Siddha texts: a literature review. J Ayurveda Integr Med 2019 Apr;10(2):131—4.
[36] Shanmugavelu M. Noi naadal Noi muthal naadal thirattu part —I. 1st ed. Directorate of Indian Medicine & Homoeopathy; 2014. p. 247.
[37] Rathinam S, Muthiah K, Parameswaran S, Tamilarasan K, Selvarajan E, Ayyasamy U. Analogy of Kaba suram with COVID-19 symptoms - a siddha literature review. Int J Ayurvedic Med 2020 Dec 9;11(4):616—21.
[39] Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care 2020 Dec;8(1):49.
[40] Hu G, Wu Y, Zhou Y, Wu Z, Wei L, Li Y, et al. Prognostic role of D-dimer for in-hospital and 1-year mortality in exacerbations of COPD. Int J Chronic Obstr Pulm Dis 2016;11:2729.
[41] Giannakodimos I, Gkountana G-V, Lykouras D, Karkoulias K, Tsakas S. The role of interleukin-6 in the pathogenesis, prognosis and treatment of severe COVID-19. Curr Med Chem 2021 Sep 8;28(26):5328—38.
[42] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020 Jan;14. 175346662093717.
[43] Thillaivanan Samraj K, Susikannamma S, Parthiban P. A pharmacological review of siddha classical preparations for the management of COVID-19 at TPEC COVID care Centre, Vellore. JPRI 2021;33(44B):504—16.
[44] Torrente-López A, Hermosilla J, Navas N, Cuadros-Rodríguez L, Cabeza J, Salmerón-García A. The relevance of monoclonal antibodies in the treatment of COVID-19. Vaccines 2021 May 26;9(6):557.
[45] Jose SP, Ratheesh M, Sheethal S, Rajan S, Saji S, Narayanan V, et al. Anti-inflammatory effect of Kaba Sura Kudineer (AYUSH approved COVID-19 drug)-A Siddha poly-herbal formulation against lipopolysaccharide induced inflammatory response in RAW-264.7 macrophages cells. J Ethnopharmacol 2022;283:114738.
[46] Halaby R, Popma CJ, Cohen A, Chi G, Zacarkim MR, Romero G, et al. d-Dimer elevation and adverse outcomes. J Thromb Thrombolysis 2015 Jan;39(1): 55—9.
[47] Cosmi B, Legnani C, Iorio A, Pengo V, Ghirarduzzi A, Testa S, et al. Residual venous obstruction, alone and in combination with D-dimer, as a risk factor for recurrence after anticoagulation withdrawal following a first idiopathic deep vein thrombosis in the prolong study. Eur J Vasc Endovasc Surg 2010 Mar;39(3):356—65.
[48] Oualim S, Abdeladim S, Elouarradi A, Bensahi I, Hafid S, Naitelho A, et al. Elevated levels of D-dimer in patients with COVID-19: prognosis value [Internet]. Pan Afr Med J; 2020 [cited 2021 Jul 28];35. Available from: https://www.panafrican-med-journal.com/content/series/35/2/105/full.
[49] Sathish T, Cao Y. What is the role of admission HbA1c in managing COVID -19 patients? J Diabetes 2021 Mar;13(3):273—5.
[50] Mishra D, Dey CS. Type-2 diabetes, a co-morbidity in Covid-19: does insulin signaling matter? Biochem Soc Trans 2021;49(2):987—95.
[51] Xu N, Chen J, Chang X, Zhang J, Liu Q, Li A, et al. nCD64 index as a prognostic biomarker for mortality in acute exacerbation of chronic obstructive pulmonary disease. Ann Saudi Med 2016 Jan;36(1):37—41.