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An open clinical evaluation of selected siddha regimen in expediting the management of COVID-19—a randomized controlled study

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ABSTRACT

Background: The corona virus disease 2019 (COVID-19), an acute respiratory disease, caused by a novel corona virus (SARS-CoV-2, previously known as 2019-nCoV), obtained worldwide attention. In this review, we explored the potential siddha strategies for COVID -19 infections.

Objectives: To evaluate the additional benefits of siddha drugs Vasanta kusumakaram mathirai, Thippili rasayanam, Adathodai manapagu and Kabasura kudineer compared to the allopathic standard treatment of care alone in COVID-19 asymptomatic, mild — moderate cases.

Materials and methods: The present study was an open label Two arm - randomized controlled interventional clinical study. The Group I patients were assigned to Siddha add on treatment whereas Group II subjects were assigned with standard treatment alone. The sample size was 100 for each group.

Result: The average number of days taken for reduction of symptoms showed significant results (P < 0.001) in Siddha add on compared with standard treatment. The real – time polymerase chain reaction (RT-PCR) investigation turned negative for 78.33% in Siddha add on and 33.33% in standard treatment after 11–14 days. Similarly, CT chest, covid pattern lung involvement percentage showed highly significant reduction (P < 0.0001) in Siddha add on treatment. In addition, Neutrophil Lymphocyte Ratio (NLR) ratio, showed significant reduction (P < 0.01) when analyzed by Wilcoxon signed rank test, and Renal, Liver parameters were within the normal limits in Siddha add on Group for 25 samples in post treatment.

Conclusion: Finally, it was concluded that Siddha add on Group showed accelerated recovery for COVID -19 patients compared to standard Group. The synergistic effect of Siddha add on with standard treatment gave more promising results in the current study of COVID -19.

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1. Introduction

An acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV), the coronavirus disease 2019 (COVID-19), has spread throughout China and received worldwide attention. On 30 January 2020, the World Health Organization (WHO) officially declared the COVID – 19 epidemics as a public health emergency of international concern.

The emergence of SARS-CoV-2, since the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 marked the third introduction of a highly pathogenic and large-scale epidemic coronavirus into the human population in the twenty-first century. As of 22 Aug 2020, a total of 22,812,419 confirmed cases globally, 29,75,701 confirmed in India, with 55,794 deaths had been reported by WHO [1]. In Tamil Nadu a total of 3,67,430 COVID cases and 2501 in death toll. Meanwhile, several independent research groups have identified that SARS-CoV-2 belongs to β-coronavirus, with highly identical genome to bat coronavirus.
pointing to bat as the natural host. The novel coronavirus uses the same receptor, angiotensin-converting enzyme 2 (ACE2) as that for SARS-CoV, and mainly spreads through the respiratory tract. Importantly, increasingly evidence showed sustained human-to-human transmission, along with many imported cases across the globe. The clinical symptoms of COVID-19 patients include fever, cough, fatigue, and a small population of patients appeared gastrointestinal infection symptoms. The elderly and people with underlying diseases are susceptible to infection and prone to serious outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm. Currently, there are few specific antiviral strategies, but several potent candidates of antiviral and repurposed drugs are under urgent investigation [2].

In this research studies, we explored the potential Siddha strategies for COVID-19 infections.

The selected Siddha regimen for COVID-19 study comprised Kabasura kudineer (KSK) and Adathodai manapagu (AM), indicated for fever and respiratory ailments [3] whereas Vasantha kasumakaram mahriru (VKM) and Thippili Rasayam (TR) were indicated for respiratory problems [4]. The drugs were chosen based on the Siddha principles of Tridosham and also their effectiveness in respiratory viral diseases. The Siddha medicines KSK and AM are quoted in classical Siddha texts, approved by Drug and Cosmetic Act, The Siddha Formulary of India, Part I, published by Department of Health and Family Welfare, Government of India.

These Siddha medicines had been widely in use for decades in the treatment for the above indicated ailments. Moreover, these medicines are currently in use and dispensed to the patients in all Government Siddha, OPD (out patient department), and IPD (in patient department) wings of Tamil Nadu. The efficacy of the medicines had also been validated scientifically in respiratory and other ailments [5–11].

The objectives of the present trial was to establish the add on benefits of selected Siddha medicines VKM, TR, AM and KSK in the management of COVID–19 diseases as Siddha regimen along with standard treatment compared with patients who have not taken the Siddha medicines but only Standard treatment alone. Other concurrent objectives was to evaluate the improvement of COVID-19 symptoms presented in patients, reduction of days in long term hospitalization as well as reduction in case fatality rate.

2. Materials and methods

This study was conducted in accordance with the intent and purpose of Good clinical practice guidelines and/or the Declaration of Helsinki, as appropriate. The study was initiated after getting Institutional Ethics Committee approval at Government Medical College, Omandurar estate campus, Chennai—02. The study protocol was registered at Central Trial Registry of India, Registration number CTRI/2020/06/025856.

2.1. Raw drugs and Siddha medicines procurement:

The drugs were manufactured in the GMP certified In-house pharmacy of Arinngar Anna Hospital of Indian Medicine, Arumbakkam, Chennai with the ingredients authenticated by the Botanist of TAMPCOL, SIDCO, Pharmaceutical campus, Aluthur, Thirupur, Kanchipuram. All the selective medicines VKM, TR, AM and KSK were funded by The Directorate of Indian Medicine and Homeopathy for the clinical trial. The clinical trial was carried out in the period of June 2020–July 2020 at Government Medical College, Omandurar estate campus, Chennai. The Dean of Omandurar Government Medical College supervised the trial.

2.2. Study design and patients recruitment:

The present study was an open label, two arm, randomized controlled interventional clinical study. The Group I patients were assigned to Siddha add on treatment whereas the Group II patients were assigned to standard treatment alone. The patients recruited for the study were COVID-19 RT-PCR +ve patients admitted in IPD. One set of patients were identified by active surveillance and contact tracing at their door steps. The other set of people who reported to the hospital were also tested. Though the swabs were collected in their doorsteps all the test were carried in the Indian Council of Medical Research (ICMR) approved laboratories with bio safety level 3 by competent lab technicians.

2.3. Sample size and randomization:

The sample size was 100 in each group. From the calculated sample size using a power of 80%, each group in the study consisted of 90 subjects giving a total of 180 subjects and an additional 10% drop out rate added with total sample size 100 each. Appropriate corrections were affected after the research instrument was pre tested. Simple random sampling method was employed. The participants were equally allocated to either Group I or Group II by computer-generated random numbers using the Stat Trek random number generator [12]. The Siddha add on Group was labelled as treatment one and standard treatment was labelled two. The upper limit of random numbers input into the Stat Trek random number generator was 200 (reflecting the sample size), with a minimum value of one and a maximum of two, representing the two groups; it allowed for duplicate entries. Thereafter, a statistician created a table of 200 entries and labelled each entry with either number one or two. Participants’ assigned number one were allocated to the Siddha add on treatment and those assigned number two were part of the standard treatment. The participants, researchers and data analysers therefore were not blinded to the allocation.

2.4. Inclusion criteria:

Age group: 18–60 years, Sex: Male and Female & Transgender. Confirmed RF- PCR test positive with asymptomatic, mild and moderate symptom patients [13].

2.5. Exclusion Criteria:

Age: Less than 18 and above 60, Pregnancy and lactating mothers, Patients with severe or critical COVID-19 infections, Mentally retarded and those who are taking psychiatric drugs, Immuno-compromised patients, Patients with co morbid disease conditions, Other viral pneumonia Patients who have received organ transplantation in the past 6 months or planning surgery were excluded clinically and based on available medical reports. Before conducting the trial, a predesigned, written informed consent form was obtained from the patients by following an explanation about the study in the local language (Tamil) and in English for those who were not familiar in local language. The study adheres to CONSORT guidelines.

2.6. Withdrawal Criteria:

Aggravation of symptoms, Intolerance to drug and development of adverse reactions during drug trial, Occurrence of any other severe illness, Incidence of any acute illness that would warrant other extensive drug treatment during the trial, Withdrawal proforma towards discontinuation of patients and adverse drug reaction
proforma was also designed to record and report any serious adverse event.

2.7. Outcomes:

Data regarding demographic particulars, lab investigation, and drug history of the patients were obtained from them in person and through their case sheets. During follow up period the symptoms were recorded telephonically. After 11–14 days of treatment, clinical assessment was mainly determined by reduction of clinical symptoms and the main parameters used for assessment were, comparing before and after treatment RT-PCR report and CT chest Ground glass opacities COVID-19 pattern (GGO) lung involvement percentage [14]. The CT scan findings were confirmed by the Head of the Radiology Department, Government Omandurar Medical College, Chennai-02. The following investigations were also undertaken, a) CBC (complete blood count) b) Blood sugar (fasting and post prandial) c) SpO2 (oxygen saturation) were taken for all the patients at the time of admission and d) RFT (renal function test) e) LFT (liver function test) for suspected patients who had clinical abnormality with relation to renal and liver diseases at the time of admission and discharge since most of them were discharged based on reduction of symptoms due to pandemic issue.

2.8. Intervention:

The Group I asymptomatic, mild, moderate patients received Siddha add on treatment. The standard treatment comprises tablets 1–7 with respective drug dosage of 1. Hydroxychloroquine, 2.Ivermectin, 3.Azithromycin, 4. Paracetamol, 5. Omez, 6.Vitamin C, 7. Zinc with clinical observation were characterised. The Siddha add on treatment included KSK.60 mL b.d. before food, VKM (130 mg) 1 tablet b.d. after food, TR 2 gms b.d. after food, AM, 15 mL b.d. with 30 mL lukewarm water after food added with the standard treatment for a duration of about 14 days with a follow up period of 14 days counted from the end of treatment (total follow up period including drug treatment and drugless follow-up is 28 days). Similarly, The Group II asymptomatic, mild and moderate patients received standard treatment alone. The outcome was measured through resolution of symptoms and recovery of patients (RT-PCR, CT chest investigations) from COVID-19 disease compared to patients taking only standard treatment between 11 and 14 days. As secondary outcome measures sub group analysis of male, female and mean age group, symptoms distribution in both groups were studied. Case fatality rate was also documented in both the groups.

2.9. Statistical analysis

The collected data were analysed using Graph Pad Prism software version 5 and SPSS 21. Demographic variables were given in frequency and percentage. Statistical analysis for gender difference was analysed using chi-square test. Age difference and average days of symptom reduction was analysed using student independent t-test. Statistical analysis for RT-PCR evaluation was done using chi-square test and relative risk was given with 95% confidence interval. Student paired t-test was used to analyse CT chest results before and after treatment. Blood investigation parameters before and after treatment were analysed for 25 samples in Siddha add on group patients using Wilcoxon signed rank test. In order to ascertain if there is any adverse reaction in vital organs like kidney and liver, renal and liver profile were recorded for 25 samples (after treatment) and expressed as mean and SD in Siddha add on group.

3. Result

A total of 212 subjects were screened for the study of which 200 subjects satisfied the inclusion criteria and 100 patients were allocated to each group in the study. In total 12 subjects dropped out and subsequently for want of resources (due to inadequate bed strength, rest were recommended to COVID-19 care centers) sixty were included in Siddha add on treatment and 30 were included in standard treatment. The enrolment, allocation, follow up and analysis scheme of the trial is depicted through consort flow diagram (Fig. 1).

The gender distribution was analysed and observed that, in Siddha add on group among 100 patients, 71 were male and 29 were female. In standard treatment group, among 100 patients analysed during the study period, 69 were male and 31 were female. Hence gender distribution was similar in both the groups according to chi-square test. The mean age of patients was observed as 42.98 in Siddha add on treatment and 45.68 in standard treatment. There was no significant difference between age group according to student independent t-test. Table 1, showed the symptoms of patients at the time of admission in Siddha add on treatment and standard treatment respectively (n = 100). In Siddha add on Group, the mean value of number of days taken for reduction of symptoms after the treatment was 3.21 and in standard treatment group, the average mean was 5.13. According to chi-square test Siddha add on group showed significant result (P < 0.001) when compared with standard treatment group. Added to this, the average number of days of hospitalization for mild symptom patients was 3–4 days and moderate symptom patients was 4–5 days respectively in Group I (Siddha add on treatment).

Fig. 1. Consort flow chart diagram.
Similarly, in Group II (standard treatment), 4–5 days for mild symptom patients and 10–11 days for moderate symptom patients and they were directed to COVID care centre for further care. Hence it was concluded that Siddha add on treatment was more effective when compared to standard treatment alone.

Table 2 showed the number of positive and negative cases confirmed using RT-PCR technique after 11–14 days treatment. The number of positive cases identified in the Group I (Siddha add on treatment) were 13 and negative cases 47 among 60 cases. Similarly, in Group II (standard treatment), the number of positive cases identified were 20 and negative cases 10 in a total of 30 cases. The positive percentage of Siddha add on treatment was 22.67% whereas standard treatment was 66.67%. So, the difference was statistically significant according to chi square test. Relative risk was 2.09. It shows that standard treatment positivity was 2 times higher than Siddha add on treatment positivity. Hence, it was concluded that Siddha add on treatment makes the patient noncontagious at earlier days itself when compared to Standard treatment (allopathic) alone.

In CT chest findings, Ground glass opacities, COVID-19 pattern (GGO) of total lung involvement percentage was taken as parameter and compared before and after treatment in patients of Siddha add on treatment and standard treatment respectively using student paired t-test. In Siddha add on Group, after CT chest results showed highly significant reduction (P < 0.0001) when compared with before CT chest results. In standard treatment Group, the after CT chest results compared with before CT chest results showed significant reduction (P < 0.001). The percentage of mean activity (represents the percentage protection of respective drug treated group) observed in Siddha add on treatment was 64.34 and standard treatment 54.39. Hence it was observed that Siddha add on treatment showed more promising results than standard treatment alone.

The Blood investigation parameters, Total count (TC), differential count (DC), Absolute lymphocyte count (ALC), Neutrophil Lymphocyte Ratio (NLR) ratio, Red blood cell (RBC), Haemoglobin (Hb), packed cell volume (PCV), and platelet count were analysed for 25 samples in Siddha add on Group before and after treatment (due to limited health professional, reagents and lockdown issue we were unable to collect the samples from all patients) and summarized in Table 3 using Wilcoxon signed rank test. ALC showed significant improvement P < 0.001 and NLR showed significant reduction P < 0.01. Platelet count showed improvement in post-test while PCV value remained unaltered in pre and post-test respectively. RBC and Hb showed insignificant reduction in post-test compared to pre-test and the P values for these were not significant. There is a general perception that some of the herbal medicines may cause renal or liver function impairment. Therefore, in order to ascertain the safety of Siddha formulations co-administered in the present study, Liver function test and renal function test (LFT, RFT) also carried out after 14 days of treatment for 25 samples in Siddha add on Group. The findings were found to be within normal range and the mean and SD were summarized in Table 4. In the trial, 2 deaths were recorded in Group II (standard treatment) and no death in Group I (Siddha add on treatment). No adverse drug reactions were reported in both the groups. The main observation noted was there was no drug interaction reactions reported in Siddha add on treatment patients. Hence, Siddha add on treatment was found to be safe in the treatment of COVID-19 infections.

4. Discussion

Indian traditional medicinal systems are considered as one of the oldest treatments in human history and it plays an important role in encountering global health care needs. Traditional Indian medicinal practices include Ayurveda, Siddha, Unani and Yoga, Naturopathy and Homeopathy, which are successfully practiced for treating various diseases. These practices came into existence 5000 years ago, and these systems have been witnessed and scripted in ancient literature [3].

Siddha medicine has served to south Indian people since ancient times and played a vital role in today’s medical care. The medicines selected as Siddha regimen in this trial had been already given for fever and respiratory ailments for decades in Tamil Nadu Government Siddha sector hospitals. Hence, repurposing the existing drugs and to utilize them in the treatment could be targeted to reduce the disease burden in this pandemic situation.

In a study by Balachander et al., 2020, it has been pointed out various herbal plants having anti-viral properties and plant-based medicines could be selected for COVID-19 infections [3]. In another study by Yang et al., 2020, a patent Traditional Chinese Medicine
(TCM) had showed ≥ 60% of patients with marked improvement and stabilization when treated for COVID-19 infections [15].

The current study evaluated the effect of integrated approach for COVID-19. The clinical results of our study showed that integrated group patients had better promising results and the treatment appears to shorten patient hospitalization days. One of the supported evidence was that the Neutrophil lymphocyte ratio, Liver function test, Renal function test parameters were found to be within normal range in integrated approach group of patients tested for 25 samples after treatment. (as health care professionals, equipment’s and reagents were limited and were unable to handle the vast number of patients who are infected) This confirms the safety profile of Siddha medicines in Group I patients. Although the composition of KSK, TR and AM are completely herbal, herbino mineral drug VKM contains one metal component Cinnabar and one mineral component Borax along with other herbal ingredients in equal ratio. Hence, in spite of having metal and mineral components as ingredients in small quantities, the co-administered Siddha regimen treatment was proved to be safe in COVID-19 patients.

Historically, traditional Siddha medicine has been proven effective in combating epidemics during dengue outbreak in Tamil Nadu. Despite of low-level evidence and unknown mechanism of action the Siddha medicine deserve attention for the management of sudden unexpected outbreaks of infectious diseases. Since this is the first study, with small sample size, implications of further research include a possible comparison of placebo with only Siddha regimen medicines to determine its efficacy. It is clear that more standard clinical trials on large scale with competent clinical investigations should be carried out scientifically to prove the efficacy of Siddha medicines for COVID-19.

5. Conclusion

The current study concludes that Siddha add on Group showed accelerated recovery for COVID-19 patients compared to standard treatment Group. The synergistic effect of Siddha add on with standard treatment gave more promising results during the entire study period of COVID-19. Furthermore, this present trial throws light on repurposing the existing drugs in traditional Siddha system of medicine to utilize them in the treatment of COVID-19.

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Conflict of interest

None.

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References

[1] World Health Organisation. Corona virus disease Covid – 19. Dashboard, updated on 22/8/2020, https://covid19.who.int/.
[2] Guo YR, Cao QD, Hong ZS, Tan YY, Chan SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7(1):11. Published 2020 Mar 13, https://doi:10.1186/s40779-020-00240-0.
[3] The Siddha Formulary of India, Part I, Department of Health and Family Welfare, Government of India, 287-331.
[4] Kuppusamy Mudaliar KN, Uthiramalayar KS, Siddha VaithiyaThirattu, 40. Indian Medicine and Homeopathy Department; 2014. p. 235-342.
[5] Veeringiri B, Jayaramayya K, Iyer M, Narayanasamy A, GiriDharan B, et al. COVID-19: a promising cure for the global panic. Sci Total Environ 2020;725:138277. https://doi.org/10.1016/j.scitotenv.2020.138277.
[6] Saravanam J, Devasia N, GopalaSatheshkumar K, Sanish Devan V, Thanga Kokila K, Sanjay M. Anti-inflammatory, antipycritic and antibacterial study of Kabasura kudineer choornam. Int J Curr Adv Res 2018;7(2):9952–7. https://doi.org/10.24327/ijcar.2018.9997.1672.
[7] Management of chikungunya through Ayurveda and siddha. New Delhi: Central Council For Research in Ayurveda and Siddha, Department of AYUSH, Ministry of Health and Family Welfare, Government of India; 2009.
[8] Priya NC, SaravananKumari P. Anti-viral activities and cytotoxicity assay of seed extracts of Piper longum and Piper nigrum on human cell lines. Int J Pharamceut Sci Rev Res 2017;44(1):197–202.

[9] Devarajan C, Walter Thomas M, Pauline Vincent C. Siddha medicines for eraippu erumal (bronchial asthma) - preliminary phytochemical and antimicrobial studies. https://www.researchgate.net.

[10] Acute and sub-acute toxicity study of venkararpam, dissertation, branch VI –nanju noolum maruthuva neethi noolum, NIS. Tambaram; September 2007.

[11] A toxicity study on linga chenduram, dissertation, branch VI –nanju noolum maruthuva neethi noolum. Palayankottai: GSMC; April 2013.

[12] Stat Trek Random number generator. From: www.stattrek.com/statistics/random-number-generator.aspx.

[13] Clinical management of COVID – 19. Interim guidance. WHO; 27 May 2020.

[14] Hani C, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, et al. COVID-19 pneumonia: a review of typical CT findings and differential diagnosis. Diagn Intervent Imag 2020;101(5):263–8. https://doi.org/10.1016/j.diii.2020.03.014.

[15] Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. Int J Biol Sci 2020;16(10):1708–17. https://doi.org/10.7150/ijbs.