Section A-Research paper
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Analysis of an Open Labelled Randomized Controlled Trial to Evaluate the Efficacy and Safety of Siddha Supplement (MAM Granules) along with Standard of Care Treatment in the management of RT-PCR Positive Pre-symptomatic COVID-19 patients at COVID-19 Care Centre, Greater Noida, Uttar Pradesh, India.

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Abstract:

Background: COVID-19 emerges as the major global healthcare challenge of this century. In March 2021 during the initiation of the study, there is no proven herbal **add-on therapy** declared to combat COVID-19. Therefore, based on evidence from Pre-Clinical Studies, we tested the safety and efficacy of polyherbal drugs from India's one of traditional medical systems i.e. Siddha Medical System namely "MAM Novel Siddha formulation" for the management of COVID-19. These Studies' outcomes will be useful to explore the appropriate add-on Siddha drug in the management of COVID-19.

Methods: Objectives: Reducing the onset of clinical symptoms in asymptomatic patients, Reduction in the duration of SARS CoV-2 viral infections and reduction of viral load from the baseline were all the primary outcomes. The secondary outcomes were to assess immunological markers, and safety profile and to document the profile of study participants

based on the Siddha principles. It was an open labelled, single centre, double arm, exploratory and comparative Randomized Controlled Trial. We recruited the RT-PCR Positive tested for COVID-19 Patients at COVID Care Centre (CCC) situated at Govt. Institute of Medical Sciences, Greater Noida, India. It was an exploratory study to evaluate the efficacy of MAM granules in Pre - symptomatic COVID-19 patients, we planned to recruit 32 participants in each group. A simple random allocation method was done. The participants were assigned into 2 groups and allocated through randomization blocks in Microsoft Excel in a 1:1 ratio in each group. During the time of enrolment, we collected data on the history of illness, socio-demographics, and clinical examination. We did a systematic clinical examination, determine adherence to interventions and assessment about any complaints and adverse events at every visit. Statistical analysis was made using standardized tests to compare the two interventional arms for both primary and secondary efficacy measures.

Results:

The study group (SG) exhibited a significant result in converting RT-PCR Positive patients to negative compared to the Control Group (CG). A statistically significant reduction in the viral load of SARS-CoV-2 was documented in the SG compared to the CG. The Mean days in relieving all these symptoms were significantly ($p<0.001$) lower in the SG (10.77±2.50) as compared to the CG (34.19±6.03. The mean change in CRP, Ferritin and LDH levels in the SG (1.74±1.54, 67.00±45.90, 155.99 ±78.90) was significantly ($p<0.001$) lower as compared to the CG (5.80±5.63, 183.58±101.14, 320.82±104.09) D-Dimer (0.44±0.53, 0.99±1.57) was found to be non-significant ($p>0.05$) among the 2 groups. The mean SpO2 was significantly($p=0.001$) (higher in the SG (97.38±1.05) as compared to the CG (95.78±2.31). In both groups, there were no adverse events (AEs) or serious adverse events (SAEs) reported until the completion of the study.

Conclusions:

Siddha polyherbal formulation "MAM Granules" emerged as significantly effective and efficacious in the management of patients with Pre-Symptomatic COVID-19 RT-PCR Positive as compared to the Standard of Care. Two weeks of following the treatment protocol also prevented the incidence of the patients becoming symptomatic of COVID-19. Large-scale multicentric studies will strengthen these findings.

Trial Registration: This trial was registered in CTRI (the Clinical Trial Registry of India) (Registration number - CTRI/2021/02/031420 on 19.02.2021). **Url of Registration: https://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=52957&EncHid=&modid=&compid=%27,%2752957det%27**

Keywords: COVID-19, Siddha Medicine, RCT, MAM Granules, AYUSH, CAM

Background:

The first case of SARS-CoV-2 virus infection was found in Wuhan, China in December 2019, (1), In January 2020, WHO announced the emergence of COVID-19 as a major health care challenge which has affected lives globally. The worldwide, healthcare community is actively seeking a proven solution for this serious health concern (2). In March 2021, during the initiation of the study, there is no proven herbal add-on medicine declared to combat COVID-19(3). On 28th Feb 2021 in India, registered cases of COVID-19 were 11,124,527(4).

AYUSH medicines especially Siddha Medicines *Kabasura kudineer, Nilavembu kudineer, Vasantha kusumakaram mathirai, Thippili rasayanam and Adathodai manapagu* played a vital role in both treatment and prophylactic aspects in the management of COVID-19(5). Signs and symptoms can correlate with *Kaba Suram* which is mentioned in ancient Siddha literature (6,7). Two RCTs were conducted at GIMS, Greater Noida (8,9) and Stanley Medical College, Chennai (10) and found effective in SARS-COV-2 viral infection control. Reducing the onset of clinical symptoms in asymptomatic patients, Reduction in the duration of SARS CoV-2 viral infections and reduction of viral load from the baseline were all the primary outcomes. The secondary outcomes were to assess immunological markers, and safety profile and to document the profile of study participants based on the Siddha principles. The trial was initiated on March 2021 which was the peak time of the COVID-19 second wave in India.

Methods:

Trial design: It was an open-labeled, single centre, double-arm, exploratory, and comparative Randomized Controlled Trial in a 1:1 ratio in each group.

Participants: Participants whom RT-PCR Positive tested for COVID-19 Patients at COVID Care Centre (CCC) situated at Govt. Institute of Medical Sciences, Greater Noida, India was recruited. They were pre-symptoms (with or without symptoms) with laboratory-confirmed COVID-19 (RT -PCR Tested Positive) aged 18-65, willing and consenting to participate in the study. They were randomly allocated by using a simple randomization technique into control and study groups. Picturized documentation of trial flow is explained in Fig.1.

Study Setting:

The trial was performed at COVID Care Centre (CCC) situated at Govt. Institute of Medical Sciences, Noida, Uttar Pradesh in India.

Interventions:

Trial Drug:

The study drug MAM Granules was a Siddha polyherbal formulation and it is brownish yellow in colour. The study drug was manufactured and procured from Central Pharmacy, Siddha Central Research Institute (CCRS), Chennai in the form of granules as a single batch for the maintenance of homogeneity. Two grams of the trial drug were given with milk along with SOC for 14 days daily in the morning and evening. Details of the ingredients of the Trial drug are mentioned in Table 1.

Control Drug:

The control group was provided Zinc and Vit. C orally for 14 days daily along with other SOC in the morning and evening.

Outcome measures:

The major outcomes were the negative conversion of SARS-CoV - 2 by 14 days, a reduction in SARS-CoV-2 Viral load at the end of the treatment period, a reduction in the incidence of clinical symptoms (fever, cough, breathlessness, etc.), and an effect in Immunology and inflammatory markers (IL6) of supplement at the end of treatment (14 days). Reduction in the incidence of complications (ARDS, other Respiratory Illnesses) & mean changes in laboratory markers like Haematological & Bio-Chemical Markers, and the occurrence of the ADR were documented as secondary outcomes.

During the entire treatment period, Clinical assessments were carried out periodically. This included an examination based on the Siddha Principles (Siddha *Udaliyal* and *Mukkuttram*). Laboratory and biochemical assessments like renal function, liver function, hemogram, inflammatory markers, electrolytes, nasopharyngeal (NP), and oropharyngeal (OP) swabs were done at baseline and on the seventh day and 14th Days. paper-based case record forms were used to document the clinical data.

Sample size:

We did not have any prior data on the efficiency of add-on Siddha formulation in the management of COVID-19. Hence, as an exploratory study of the efficiency of MAM Granules on asymptomatic COVID-19 patients, we decided to recruit 32 participants in each of the two groups in a 1:1 ratio in each group. (30)

Randomization:

Randomization was performed following the Simple random allocation method. After the assessment of eligibility and informed consent procedures, the participants were assigned into two groups and allocated in a 1:1 ratio through randomization blocks in Microsoft Excel by a Statistician in each group. (30)

Blinding:

Investigators and participants were not blinded. It was an open labelled.

Statistical analysis:

By using standardized tests to compare the two interventional arms for primary and secondary efficacy measures, Statistical analysis was made. The safety of the study participants was also analyzed. To identify predictors of response, Regression analysis was done. Clinical symptoms, subjective parameters, and Laboratory parameters were subjected to univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) 15.0 version with appropriate statistical methods. A total number of 64 participants, 32 each were recruited in a 1:1 ratio in each group.

Results:

Trial participants were recruited and admitted at the COVID-19 Care Centre (CCC), Govt. Institute of Medical Sciences, Greater Noida, Uttar Pradesh, India as per Uttar Pradesh State Government guidelines. During the period of recruitment (March 2020 – June 2020), 93 participants were screened and 64 were enrolled into the study who were consented to participate in this study.

Except for age and gender, all other baseline characters were monitored similarly in both groups (study and control groups) (Table 2). There were no significant differences in Biochemical parameters at baseline in both groups.

The study group showed a significant result in converting RT-PCR positive participants to negative compared to the CG. In the SG compared to the CG, a statistically significant reduction in the viral load of SARS-CoV-2 was documented.

As compared to the control group, the mean changes in IL6, CRP, Ferritin, and D-Dimer levels in the study group were significantly lower and LDH levels were found to be non-significant ($p>0.05$) among the two groups.

The mean days in relieving all symptoms were significantly ($p<0.001$) lower in the SG (10.77±2.50) as compared to the CG (34.19±6.03). The mean change in CRP , Ferritin and LDH levels in the SG (1.74±1.54, 67.00±45.90, 155.99 ±78.90) was significantly ($p<0.001$) lower as compared to the CG (5.80±5.63, 183.58±101.14, 320.82±104.09). The mean changes in IL6 levels in the SG (23.03± 22.94) were significantly($P=0.001$) better as compared to the CG (53.92±46.43). The mean SpO2 was significantly($p=0.001$)(higher in the SG (97.38±1.05) as compared to the CG (95.78±2.31). In both groups, there were no adverse events (AEs) or serious adverse events (SAEs) reported until the completion of the study.

None of the parameters viz Liver Function Test (LFT) and Renal Function Test (RFT) parameters showed a significant difference in both the SG and CG at the time of completion of the treatment ($p>0.05$) and data is condensed in Table 3.

In both groups, there were no adverse events (AEs) or serious adverse events (SAEs) reported until the completion of the study

Table 1: Composition of MAM Siddha Granules

S.No	Botanical Name	Siddha Name	Family Name	Part Used
1	*Curcuma longa*	*Manjal*	Zingiberaceae	Route Tuber
2	*Withania somniefera*	*Amukkara*	Solanaceae	Route Tuber
3	*Piper nigrum*	*Milagu*	Piperaceae	Dry Fruit

Table 2: Baseline characteristics of the Study (SG) and Control (CG) group

Characteristics		Study group (n=32)	Control Group (n=32)
Age (in years)	Mean ± S.D	36.45±11.52	40.09±12.72
Gender	Male	16	18
	Female	16	14
Occupation	Student	3	1
	Homemaker	10	10
	Unemployed	16	14
	Employed	3	7
Education	Higher Secondary	2	3
	Diploma	10	11
	Degree	11	9
	Postgraduate	9	9
History of Exposure	COVID-19 contact	15	18
	Do not know	17	14

Table 3: Biomedical and immunological parameters (Mean ± S.D) in both groups Before and After Treatment

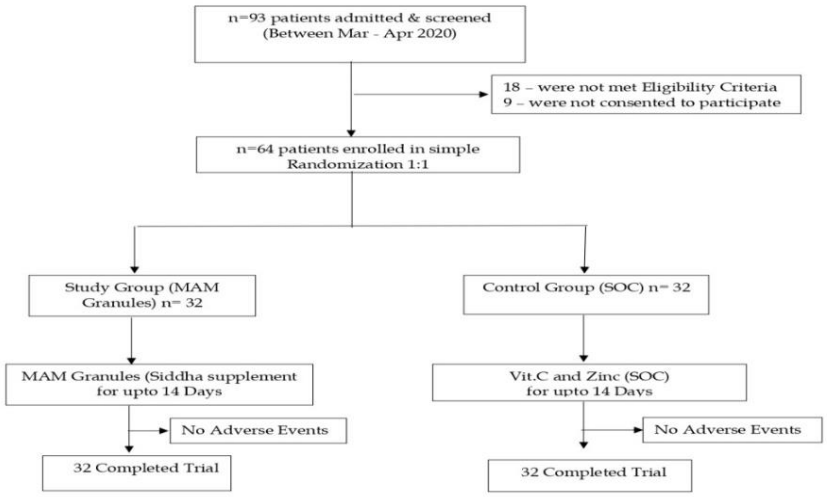
Investigations	Study Group (SG) (n=32)		Control Group (CG) (n=32)	
	Baseline	End Point	Baseline	End Point
I. Liver Function Test				
Bilirubin Total	0.79±0.41	6.72±0.38	0.93±0.38	0.79±0.40
Bilirubin Direct	0.19±0.10	0.20± 0.09	0.21± 0.09	0.21±0.10
Bilirubin Indirect	0.6±0.32	0.52±0.36	0.72±0.36	0.57±0.30

SGOT	29.93±9.16	32.21±14.12	32.21±14.12	30.00±9.73
SGPT	23.58±7.91	22.70±7.08	23.46±8.84	22.08±9.20
Total protein	6.69±1.05	6.91±1.09	6.89±1.14	6.34±1.06
Albumin	3.48±0.58	3.51±0.65	3.58±0.64	3.25±0.51
Globulin	3.20±0.62	3.4±0.64	3.31±0.77	3.09±0.71
II. Renal Function Test				
Urea	25.06±5.41	26.51±7.26	26.31±7.07	26.5±6.42
Creatinine	0.88±0.14	0.87±0.12	0.88±0.12	0.88±0.11
III. Anti-inflammatory and other markers				
IL 6	113.99±131.89	23.02±22.94	89.35±123.76	53.91±46.43
CRP	4.56±5.47	1.74±1.54	5.84±6.49	5.80±5.63
LDH	282.55±114.79	155.99 ±78.90	314.74±104.64	320.82±104.09
D-Dimer	1.03±1.84	0.44±0.53	0.57±1.73	0.99±1.57
Ferritin	132.34±102.91	67.00±45.90	94.03±64.82	183.58±101.14

Table 4: Duration of the symptoms (Mean ± S.D) in both Study (SG) and Control(CG) groups

Name of the Symptoms (No. of Days Total)	**Study group (n=32) Mean ±SD**	**Control Group (n=32) Mean ±SD**
Fever	3.58±0.92	6.15±1.32
Sore Throat	1.45±1.89	3.87±2.90
Cough	0.64±1.19	3.46±3.63
Diarrhoea	None	0.5± 1.01
Weakness	4.0±0	14.31±2.23
Shortness of Breath	1.10±1.58	5.88±3.48

Fig.1: Flow chart of the Trial



Discussion:

This study was conducted in Uttar Pradesh, India in February 2022 when the peak stage of the 2nd wave in India. Tracing and treating Pre-Symptomatic RT – PCR Positive COVID-19 patients was the toughest duty and that was effectively managed by healthcare workers in India. Utilization of AYUSH medicines for the treatment and management of this disease, was helped along with western medicine as an integrative therapy. Siddha classical preparations like *Kaba Sura Kudineer* and *Nilavembu Kudineer* were found effective in COVID-19 based on previous studies conducted on the same site (8,9). This study was executed to find out the role of Siddha add-on medicine especially MAM Granules in the management of COVID-19 along with Standard of Care as an add-on therapy.

Lots of culinary spices have been used based on their natural healing properties in Siddha. Individual ingredients of MAM Granules have already exhibited effective anti-viral, anti-Inflammatory, anti-dote, antioxidant, Anti – Tussive and Expectorant activities in recent Preclinical studies. (11, 12, 13, 14,15,16,17,18).

A Pre-Clinical Molecular docking study shows that "curcumin" in Turmeric and "piperine" in Black pepper, have the potency to inhibit the main protease (M-Pro in SARS-COV-2 Viruses. Another Docking study confirms the inhibition activity of "piperine" at ACE2 Receptor, SPIKE PROTEIN RBD, AND TMPRSS2 and another study proves "Withanone" from *Withania Somnifera,* inhibits the SARS COV-2 Virus entry into the cells by disrupting interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor. Some other in-silico studies also confirm the inhibition activities of constituents of Turmeric, Ashwagandha and Black pepper (19,20,21,22,23).

The preliminary, pre-clinical studies were carried out to identify the anti-viral activities of the MAM Granules at the International Centre for Genetical Engineering and Biotechnology (ICGEB), New Delhi. The results have shown that the MAM Granules had adequate anti-viral properties in Cell line studies conducted for SARS-COV-2 and CHIKV viruses.

The safety profile of the MAM Granules to know the toxic effects if any in animal models was done at Dabur Research Foundation (DRF), Mohan Estate, Ghaziabad, Uttar Pradesh. The outcome of the studies revealed that consumption of MAM Granules up to 2000mg/kg had not produced any toxic symptoms in animal models. So, based on Acute Oral Toxicity studies, it was inferred that MAM Granules are safe for human consumption.

Our trial found that integrative management of MAM Granules along with SOC (Zinc + Vit. C) Supplements reduced the hospital stay time and viral load levels significantly in Pre-Symptomatic RT – PCR Positive COVID-19 patients within 7 days. The cycle threshold (Ct) values in RT-PCR were evaluated for 4 times (at baseline (Day 0), Day 7, and Day 14). results are summarized in Table 4. A statistically significant reduction in the viral load of SARS-CoV-2 was recorded as the outcome of the study.

The increased inflammatory reaction is most commonly notable due to the host immune response in our human body in SARS-COV-2 viral infection, (24). This is the major cause of making the condition to severe level (25,26). It is also noted that increased levels of IL6 and other inflammatory markers are common in COVID-19 infections (27,28). Our study showed

that there was no significant difference in baseline mean values on IL6, CRP, LDH, D-Dimmer and Ferritin but there was a significant difference in endpoint mean values on IL6, CRP, LDH, D-Dimmer and Ferritin. The data were listed in Table 3

We can summarize that MAM Granules have significant efficacy as an add-on therapy along with SOC within the minimum sample size. Moreover, in considering palatability and easy consumption compared to other existing Siddha medicines, MAM Granules were found to be the better choice.

Limitations:

As an exploratory study, the sample size was limited. However, randomization and comparative arms are the strengths of the trial. This study is providing preliminary information that may be useful to take it to the next stage of larger multicentric studies.

Note: The mean age difference between the two groups is 4. Further studies will be planned with the stratified randomization method to avoid the difference between the groups.

Conclusions:

Siddha polyherbal formulation "MAM Granules" emerged as significantly effective in the management of Pre-Symptomatic COVID-19 RT- PCR Positive as compared to Allopathy Standard of Care. Two weeks of following the treatment protocol also prevented the incidence of the patients becoming symptomatic of COVID-19. Even though the sample size is limited, the efficiency of MAM granules along with SOC compared to only SOC alone has been confirmed exposing affirmative results. This trial also complies with the National Health Policy 2017 of integrative approaches to western medicines with traditional systems of Medicines, especially with Siddha medicines. The outcome of this trial encourages the integration of Siddha medicines with western medicines in tackling pandemics like COVID-19 and in the repurposing of existing Siddha drugs. A large-scale, multi-centric clinical trial can help bring about its boom and reproducibility.

Recommendations:

1. MAM Granules can be promoted as an add-on medicine along with other Siddha and western medicines for the management of COVID-19.
2. MAM Granules may also promote as a prophylactic add-on Siddha medicine for those who as exposed to SARS-COV-2 Viral infections.
3. Pre – Clinical studies of MAM Granules not only showed the anti-viral activities against SARS – COV-2, but also in CHIKV Virus. So, it can be promoted as an anti-viral Siddha medicine along with other western medicines as an integrative therapy.

Trial Registration: This trial was registered in CTRI (the Clinical Trial Registry of India) (Registration number - CTRI/2021/02/031420 on 19.02.2021). **Url of Registration: https://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=52957&EncHid=&modid=&compid=%27,%2752957det%27**

List of Abbreviations

AEs - Adverse Events
ARDS - Acute Respiratory Distress Syndrome
BA - Bronchial Asthma
CCRSs - Central Council for Research in Siddha
CKD - Chronic Kidney Disease

CRP - C-Reactive Protein
CTRI - Central Council for Research in Siddha
COVID 19 - Coronavirus Disease
CT Value - Cycle Threshold Value
DM - Diabetes Mellitus
DSMB - Data Safety and Monitoring Board
EC - Ethics Committee
GCP - Good Clinical Practice
GIMS - Government Institute of Medical Sciences
GFR - Glomerular Filtration Rate
HT - Hypertension
HPTLC - High Performance Thin Layer Chromatography
ICU - Intensive Care Unit
IL6 - Interleukin 6
ICMR - Indian Council for Medical Research
LDH - Lactate Dehydrogenase
LFT - Liver Function Test
mmHg - millimetre of mercury
mg/L - micrograms per liter
mg/dL - milligrams per decilitre
NKA - National Kidney Association
ng/mL - nanograms per milliliter
PPVC - Peripheral Pharmacovigilance Center
pg/mL - Picogram per milliter
RFT - Renal Function Test
ECG - Electrocardiogram
RT PCR - Reverse Transcription Polymerase Chain Reaction
SD - Standard Deviation
SARS COV 2 - Severe Acute Respiratory Syndrome Coronavirus 2
SAE - Serious Adverse Events
TLC - Thin Layer Chromatography
OECD - Organisation for Economic Co-Operation and Development
U/L - Units per liter

Declarations:

Ethics approval and consent to participate: The trial received ethical approval from the Institutional Ethics Committee of Siddha Clinical Research Unit, Safdarjung Hospital, New Delhi on 17.02.2021. Written consent was taken from all eligible and willing participants before they participate in the trial. No deviations from protocol were approved by Ethics Committee and the trial has been registered in the Clinical Trial Registry of India prospectively.

Consent for Publication: Not Applicable.

Availability of Data and Materials: All participant data will be kept confidential and personal identifiers of the study participants will not be disclosed to the public. Only the Investigator will have access to the trial data. All the procedures will be carried out in adherence to Good Clinical Practices (GCP). The monitor will have access to the study documents.

Competing Interests: The authors declared that they don't have any competing interests.

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Author's Contribution: MR, and AS conceived the concept of the study. MR, AS and VN conducted and completed the study at the trial site. VG Contributed to incorporating all lab investigations. MR, AS, VN, SS, RU, VG and SS contributed to Protocol writing. RG, KK, JK and SP gave their inputs to finalize the Study Protocol. MR, KM, AV, and NPV contributed to the manuscript writing and finalization. JK and NPV aided the Statistical analysis. This protocol is read and approved by all authors who mentioned it in the manuscript.

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Author's Information: AS, SS, RU, VG and SS possess a background in western medicine. MR, SP, KM, KK, AV and VN possess a background in the Siddha system (An Ancient Traditional medical system of India).

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