Journal of Ayurveda and Integrative Medicine 13 (2022) 100469

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

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

Case Report

Repurposing Siddha mercurial drug for mild to moderate COVID-19 – Case series and exploration of its chemical profile

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ARTICLE INFO

Article history:
Received 27 March 2021
Received in revised form
5 June 2021
Accepted 14 June 2021
Available online 30 June 2021

Keywords:
Ayurveda
Siddha
Traditional medicine
Mercury
COVID-19
SARS-CoV-2

ABSTRACT

Vajra kandi maathirai (VKM) is a mercury-based traditional Siddha drug used to treat various types of fevers and inflammatory diseases. We report our experience of using VKM successfully in the treatment of 5 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients along with its chemical profile. A family comprising of 5 members, with age ranges between 13 and 77, both male and female, one with pre-existing renal impairment, SARS-CoV-2 positive with mild to moderate category were treated with VKM along with the specific dietary practice. The drug was consumed at home quarantine. Real-Time RT-PCR from oropharynx swab, X-ray/CT scan chest, hematology, renal function, liver function, body temperature, and oxygen saturation were assessed. Blood parameters were repeated after completion of therapy to assess the safety aspect of mercury drug. With the first dose, improvement in the oxygen saturation was observed. Within 3 days of therapy, all symptoms (fever, body pain, cough, and loss of taste) were normalized and the Real-Time RT-PCR was negative for COVID-19. There were no observed side-effects and any damage to kidneys and liver were not observed. Chemical profile of the drug was done using gas chromatography-mass spectrometry and inductively coupled plasma mass spectrometry. The drug contains 22% of mercury along with a 9-Octadecenoic acid-(E), 1H-Imidazole, 4,5-dihydro-2-(phenylmethyl), and 9,12-Octadecadienoic acid (Z,Z)- as major organic compounds. VKM might be a safe drug to manage COVID-19 patients. Rigorous research is required in larger population and also for drug discovery.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the ongoing outbreak of coronavirus disease 2019 (COVID-19) globally. The transmission rate is very high and many of the transmitted cases are in the asymptomatic or mild stage. Moderate phase patients present cough and shortness of breath, whereas the severe phase patients have the septic shock with multi-organ failures [1]. India and China have added traditional medical systems along with conventional treatment protocol as an integrative approach to prevent and treat SARS-CoV-2 infection [2,3].

The traditional Siddha medical system, established by Tamil yogis (Siddhar) classifies the diseases into 4448 types and also describes their specific treatment modalities [4]. Siddhar Agastyar (Father of this medical system) and Siddhar Yugi have authored two books exclusively for fever, named as *sura nool* (Textbook on Fever) and *kaaviya sura nool* (Treatise on Pyrexia-ology) respectively. These books describe 64 different types of fevers and their specific therapies. They mention 276 different etiologies for fevers that include post-partum infection (*pirasava pani*), influenza (*jalathosha suram*), smallpox/chickenpox infection (*vaisoori*), pyrexia of unknown origin (*maha suram*), malaria (*murai kaaichal*), acute pneumonia (*kaasa suram*), acute severe viral infections (*visha suram*,

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Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2021.06.009

natchu suram), etc. All the viral infections associated with skin lesions are categorized under *vaisoori* and *ammai* categories. All the complicated fever types with different stages of multi-organ failures are categorized under *Janni* (13 types) category. Extensive documentation has been done for various types of fevers and their specific treatments. External oil application, herbal steam inhalation, herbal powder snuffing, herbal decoction (aqueous extracts), syrups, tablets, dietary practices, metal/mineral based drugs, and animal origin drugs are used in Siddha to treat fevers [5,6].

2. Historical view of *Vajra kandi maathirai*

Siddhar Patanjali (lived between 500 BC and 800 A.C) [7] is the Father of Yoga, who had also authored many Siddha books and he described a mercury-based *Vajra kandi maathirai* (VKM) (anti-fever pill) for the treatment of all kinds of fevers. The *Vajra* (*vajram*) mean hardness/strongness like diamond or hardcore, *kandi* means a rebuke or condemn or denounce without fail and *maathirai* means tablet or pill. So, the VKM means a pill that can denounce strongly without fail against life-threatening conditions. The preparation method, indications and dietary practices during the therapy have been described in detail in a Siddha literature "*Siro Rathina Nadana kaandam*" [8], written during the 17th–18th century by an unknown Siddha practitioner, and this palm manuscript was preserved in Tamil Nadu Archeology Department [8]. This pill is indicated for all types of acute, severe or chronic fevers (64 types of *suram*) with or without multi-organ failure (*janni*) [9,10].

The same drug was used successfully by a traditional Siddha Vaidyar Kannusamy Pillai (lived during 1875–1946) and found to be very effective in the following conditions such as uncontrolled fevers, chronic fevers (*thosham* in Siddha), pneumonia, fever with multiple organ failures (*janni*), lymphomas at the groin (*araiyaappu*), lymphoma around neck (*kanda maalai*), infectious discharge in the urethra (*vellai*), severe inflammation and pain in major joints (*mega kudaichchal*), small joint inflammation due to autoimmune causes (*kanu vaatham*), infectious orchitis (*virai vaatham*), infected ulcers (*pun purai*), and meningitis (*moorchai vaayu*) [11]. During 1950, the retired Judge Dr.Balaramaiah from Chennai, India documented the successful practices of this drug by many local Siddha vaidyars for the above-mentioned conditions [12].

3. Repurposing VKM for COVID-19

Even now, the same drug is being prescribed by many Siddha physicians for life-threatening infectious (viral, bacterial) conditions, inflammatory conditions, and autoimmune diseases. Based on the prior experiences, Siddha practitioners have proposed to use this drug for treating SARS-CoV-2 [9]. So far, no scientific literature is available on its clinical efficacy in COVID-19 cases, safety, and chemistry. In this manuscript, we report the efficacy of VKM in 5 cases with SARS-CoV-2 infection, along with its safety, and chemical profile.

3.1. Case presentation of COVID-19 infection in the family

A family with 5 members comprising of the grandmother (77 years old - patient 1), father (45 years old - patient 2), mother (43 years old - patient 3), and two daughters (18 and 13 years old - patients 4 and 5) were living at Chennai, India.

On 16th and 18th May 2020, patients 1 and 2 developed a high fever and body pain. With the help of paracetamol, fever was controlled; however, the body temperature varied between 102 and 105 °F. The patient 1 was having additional loss of taste sensation, whereas patient 2 was having tiredness as well as cough. She had a history of hypertension for 20 years, hypothyroidism for 13 years, and chronic kidney disease for 3 years for which she was taking medications. Since fever was persisting, both of them (patient 1 and 2) visited the nearby hospital on 19th May 2020 and their nasopharyngeal/oropharyngeal swab was collected for the SARS-CoV-2 test that showed a positive.

3.2. Real-time RT-PCR and oxygen saturation

The Real-time RT-PCR test was performed in Hitech Diagnostic Center - Chennai, an Indian Council for Medical Research approved ISO 9001:20015 certified laboratories (ICMR Registration number: HDCGHD001). The COVID-19 test was done by ICMR/FDA/CE-IVD approved kits, which includes the E-gene and RdRP gene of SARS-CoV-2 from nasopharyngeal/oropharyngeal swab. Oxygen saturation was recorded at the hospital on the first day, followed by at home by the pulse oximeter fingertip device (Delite FINGERTIP Pulse Oximeter, model: SUS-999).

4. Patient - 1 has pre-existing chronic renal failure

With the age of 77, her renal function markers in serum (urea, creatinine, and uric acid) levels were elevated (Table 1).

5. All five got COVID-19 positive

On 19th May 2020, patients - 3, 4, and 5 also developed fever (ranges between 100 and 103 °F), tiredness, and headache. All of five members consumed paracetamol tablets as self-medication.

6. Chest evaluation and blood parameters

Since the fever continued, all the five patients visited the hospital on 21st May 2020 with acute febrile illness. Patients-3, 4, and 5 also underwent RT-PCR test from nasopharyngeal/oropharyngeal swab for SARS-CoV-2 that showed positive result. X-ray chest, blood cell counts, and liver-renal function test were also performed. Since patient-1 was having cough, plain CT chest was performed, which showed the multiple patches of ground-glass opacities in all the lobes of both the lungs and crazy paving pattern in right lower lobe with CT severity score of 11. There was no pleural fluid and all other structures were normal. X-ray chest of patient-4 showed the subtle patchy opacities in the left lower zone, but clinically there was no cough or other lung symptoms (Table 1, Fig. 1), whereas the X-ray was normal for rest of the family members.

7. Allopathic treatment and home quarantine

All of them were advised for home quarantine with daily monitoring of body temperature and oxygen saturation. They were prescribed drugs for symptomatic management. Elder daughter additionally received probiotics since she was having diarrhea.

7.1. SpO2 reduction, fever, and cough for 10 days in patient-1 (Table 1)

The cough and fever were increasing in patient-1 for > 10 days, despite receiving the medications for symptomatic management. There was no satisfactory reduction in symptoms of all the family members. Hence, all of them visited the physician on 25th May 2020. Among them, patient-1 presented with the vitals of elevated body temperature 99.3° F, BP 110/70 mmHg, heart rate 106/min, respiratory rate-18/min, and SpO2 82%. The physician kept her under observation in hospital till night, but fever and cough were uncontrolled, the breathing difficulty was worsening gradually,

Table 1
The clinical feature, diagnosis, treatment and toxicity assessment of the family members.

Date	Clinical features, comorbid, mediation history, lab investigations	Treatment
Grandmother: 77, Female (patient 1)		
18 May 2020	Fever (102-105 °F), body pain, loss of taste Comorbid: hypertension for 20 years, hypothyroidism for 13 years, chronic kidney disease for 3 years Medication history: Amlodipine + atenolol, Thyroxine sodium, Vitamin supplements (Vitamin D3, folic acid)	Paracetamol
19 May 2020	Fever (100-103 °F), body pain, loss of taste Real Time RT-PCR test for COVID-19: E-gene: Positive, RdRP-gene: Positive Renal function (mg/dl): Urea-46, Creatinine-1.9, Uric acid - 6.3	Paracetamol
21 May 2020 to 25 May 2020	Fever (102 °F), body pain, loss of taste HR 64/min, SpO2 94%, RR 20/min, BP 110/80 mmHg Hematology: Hb −11.1, WBC-4.54, N-41, L-48, ALC-2179, PLT − 1.11 X-ray chest: Normal	Paracetamol Vitamin C Zincovit (multivitamin)
26 May 2020 to 29 May 2020	SpO2 95%. Fever, body pain, loss of taste − reduced after VKM	VKM 26–28 May − t.i.d. 29 May − b.d. (11 doses in 4 days)
02 June 2020	Real Time RT-PCR test for COVID-19: E-gene: Negative, RdRP-gene: Negative	−
11 June 2020	Hematology: Hb-9.6, PCV-30, RBC-3.41, MCV-87, MCH-28, MCHC-32, WBC-4.6, N-53, L-44, E-3, ESR − 09 (½ hr.) & 20 (1 h), PLT − 1.09 Glucose, Renal function (mg/dl): Glucose-85, Urea − 47, Creatinine − 2.4, Uric acid − 8.7, Calcium − 9.0, Phosphorus − 3.8 Serum electrolytes (mEq/L): Sodium − 135, Potassium − 5.2, Chloride − 99, Bicarbonate − 22 Liver function: SGOT − 28 U/L, SGPT - 20 U/L, Alkaline phosphatase − 71 U/L, Total bilirubin − 0.48 mg/dl, Direct bilirubin − 0.09 mg/dl, Indirect bilirubin − 0.39 mg/dl, Total protein − 6.9 gm/dl, Albumin − 3.7 gm/dl, Globulin − 3.2 gm%, A.G ratio − 1.2	−
Father: 45, Male (patient 2)		
16 May 2020	Fever (102 - 105 °F), body pain, tiredness and cough Comorbid: Nil, Medication history: Nil	Paracetamol
19 May 2020	Fever (100 - 105 °F), body pain, tiredness and cough BP 110/70 mmHg, PR- 108/min, RR- 18/min, Real Time RT-PCR test for COVID-19: E-gene: Positive, RdRP-gene: Positive	Paracetamol
21 May 2020 to 24 May 2020	Fever (100.4 - 105 °F), body pain, tiredness and cough HR 108/min, SpO2 81%, RR 18/min, BP 110/70 mmHg Hematology: Hb-11.5, PCV-34, WBC-4.97, N-72, L-22, ALC-1093, PLT − 1.57 CT-Chest: Multiple patches of ground glass opacities in all the lobes of both the lungs. Crazy paving pattern in right lower lobe. CT severity score of 11	Paracetamol, Sulbutiamine, Vitamin C, Zincovit (multivitamin)
25 May 2020	Morning: Fever (99.3° F), body pain, tiredness, cough, HR 108/min, SpO2 82%, RR 18/min, BP 110/70 mmHg Night: Fever (105° F), HR 106/min, SpO2 82%, RR 18/min, BP 110/70 mmHg	VKM 25 May − h.s., 26–28 May − t.i.d.
26 May 2020 to 1 June 2020	Morning: Fever (103° F), SpO2 90%, significant reduction in body pain, cough and tiredness	29–30 May − b.d. 31 May − 1 June − o.m. (16 doses in 8 days)
02 June 2020	Real Time RT-PCR test for COVID-19: E-gene: Negative, RdRP-gene: Negative	−
11 June 2020	Hematology: Hb-11.3, PCV-37, RBC-3.6, MCV-102, MCH-31, MCHC-31, WBC-6.6, N-72, L-25, E-3, ESR − 08 (½ hr.) & 20 (1 h), PLT − 2.65, Glucose, Renal function (mg/dl): Glucose-92, Urea − 35, Creatinine − 1.4, Uric acid − 7.0, Calcium − 9.1, Phosphorus − 3.5 Serum electrolytes (mEq/L): Sodium - 136, potassium − 4.9, chloride - 101, bicarbonate - 23 Liver function: SGOT − 27 U/L, SGPT - 30 U/L, Alkaline phosphatase − 80 U/L, Total bilirubin − 0.65 mg/dl, Direct bilirubin − 0.10 mg/dl, Indirect bilirubin − 0.55 mg/dl, Total protein − 7.0 gm/dl, Albumin − 3.9 gm/dl, Globulin − 3.1 gm%, A.G ratio − 1.3	−
Mother: 43, Female (patient 3)		
19 May 2020	Fever (100 °F), tiredness and headache Comorbid: Nil	Paracetamol
21 May 2020	Fever (100 °F), tiredness and headache HR 84/min, SpO2 100%, RR 20/min, BP 120/80 mmHg Hematology: Hb − 10.7, WBC-5.08, N-44, L-50, ALC-2540, PLT − 3.24 X-ray chest: Normal	Paracetamol, Livogen Z (Ferrous fumerate + Folic acid + Zinc sulphate)
22 May 2020 to 25 May 2020	Fever (100 °F), tiredness and headache, SpO2 98%, Real Time RT-PCR test for COVID-19: E-gene: Positive, RdRP-gene: Positive	Paracetamol, Livogen Z (Ferrous fumerate + Folic acid + Zinc sulphate)
26 May 2020 to 28 May 2020	SpO2 98%. fever (100 °F), tiredness and headache − reduced after VKM	VKM 26 - 28 May - t.i.d. (9 doses in 3 days)
02 June 2020	Real Time RT-PCR test for COVID-19: E-gene: Negative, RdRP-gene: Negative	-
11 June 2020	Hematology: Hb-10.3, PCV-32, RBC-4.25, MCV-76, MCH-24, MCHC-32, WBC-7.0, N-58, L-39, E-3, ESR − 09 (½ hr.) & 20 (1 h), PLT − 3.16, Glucose, Renal function (mg/dl): Glucose-82, Urea − 16, Creatinine − 0.8, Uric acid − 3.7, Calcium − 9.0, Phosphorus − 3.7 Serum electrolytes (mEq/L): Sodium − 137, Potassium − 4.0, Chloride − 101, Bicarbonate − 24 Liver function: SGOT − 21 U/L, SGPT - 23 U/L, Alkaline phosphatase − 94 U/L, Total bilirubin − 0.50 mg/dl, Direct bilirubin − 0.10 mg/dl, Indirect bilirubin − 0.40 mg/dl, Total protein − 7.1 gm/dl, Albumin − 3.7 gm/dl, Globulin − 3.4 gm%, A.G ratio − 1.1	-

(*continued on next page*)

Table 1 (*continued*)

Date	Clinical features, comorbid, mediation history, lab investigations	Treatment
Elder daughter: 18, Female (patient 4)		
19 May 2020	Fever (102 °F), tiredness, diarrhea and headache Comorbid: Nil	Paracetamol
21 May 2020	Fever (99.2–102 °F), tiredness, diarrhoea and headache HR 98/min, SpO2 100%, RR 20/min, BP 110/70 mmHg Hematology: Hb – 12.3, WBC-6.2, N-62, L-34, ALC-2111, PLT – 2.28 X-ray chest: Subtle patchy opacities in left lower zone	Paracetamol, Bifilac Tablet (probiotics)
22 May 2020 to 25 May 2020	Fever (102 °F), SpO2 97%, tiredness, diarrhoea, and headache Real Time RT-PCR test for COVID-19: E-gene: Positive, RdRP-gene: Positive	Paracetamol, Bifilac Tablet (probiotics)
26 May 2020 to 28 May 2020	SpO2 98%. Fever, tiredness and headache – reduced after VKM	VKM 26 - 28 May - t.i.d. (9 doses in 3 days)
02-06-2020	Real Time RT-PCR test for COVID-19: E-gene: Negative, RdRP-gene: Negative	–
11-06-2020	Hematology: Hb-11.4, PCV-34, RBC-4.18, MCV-82, MCH-27, MCHC-33, WBC-4.7, N-55, L-42, E-3, ESR – 06 (½ hr.) & 15 (1 h), PLT – 1.81, Glucose, Renal function (mg/dl): Glucose-81, Urea – 20, Creatinine – 0.9, Uric acid – 3.0, Calcium – 9.4, Phosphorus – 3.5 Serum electrolytes (mEq/L): Sodium – 139, Potassium – 3.9, Chloride – 101, Bicarbonate – 22 Liver function: SGOT – 19 U/L, SGPT - 20 U/L, Alkaline phosphatase – 72 U/L, Total bilirubin – 0.40 mg/dl, Direct bilirubin – 0.09 mg/dl, Indirect bilirubin – 0.31 mg/dl, Total protein – 7.4 gm/dl, Albumin – 3.9 gm/dl, Globulin – 3.5 gm%, A.G ratio – 1.1	–
Younger daughter: 13, Female (patient 5)		
19 May 2020	Fever (99 – 100 °F), tiredness and headache Comorbid: Nil	Paracetamol
21 May 2020	Fever (100 °F), tiredness and headache HR 104/min, SpO2 98%, RR 20/min, BP 120/70 mmHg Hematology: Hb – 11.6, WBC-5.8, N-58, L-38, M–4, ALC-2204, PLT – 2.87 X-ray chest: Normal	Paracetamol
22 May 2020	Fever (100 °F), SpO2 97%, tiredness and headache Real Time RT-PCR test for COVID-19: E-gene: Positive, RdRP-gene: Positive	Paracetamol
26 May 2020 to 28 May 2020	SpO2 98%. Fever, tiredness and headache – reduced after VKM	VKM 26 - 28 May - t.i.d. (9 doses in 3 days)
02-06-2020	Real Time RT-PCR test for COVID-19: E-gene: Negative, RdRP-gene: Negative	–
11-06-2020	Hematology: Hb-11.2, PCV-35, RBC-4.84, MCV-72, MCH-23, MCHC-32, WBC-10.3, N-70, L-28, E-2, ESR – 09 (½ hr.) & 20 (1 h), PLT – 2.40, Glucose, Renal function (mg/dl): Glucose-90, Urea – 15, Creatinine – 0.6, Uric acid – 3.2, Calcium – 9.4, Phosphorus – 3.2 Serum electrolytes (mEq/L): Sodium – 140, Potassium – 3.8, Chloride – 98, Bicarbonate – 23 Liver function: SGOT – 17 U/L, SGPT - 16 U/L, Alkaline phosphatase – 122 U/L, Total bilirubin – 0.37 mg/dl, Direct bilirubin – 0.7 mg/dl, Indirect bilirubin – 0.30 mg/dl, Total protein – 6.9 gm/dl, Albumin – 3.9 gm/dl, Globulin – 3.0 gm%, A.G ratio – 1.3	–

Hb- Haemoglobin in gms/dl, PCV – packed cell volume in %, RBc – total red blood cells millions/cmm, MCV – mean corpuscular volume/mean cell volume fml, MCH – mean corpuscular hemoglobin pg, MCHC – mean corpuscular hemoglobin concentration g/dl, WBC – Total white blood cells in 10^3 cells/cumm, N – nuetrophiles %, L – lymphocyte %, E – eosinophil %, ESR - erythrocyte sedimentation rate, ALC - absolute lymphocyte count, M– Monocyte, PLT –platelet 10^5 cells/cumm, b.d. – twice daily, h.s.- at bedtime, t.i.d.-three times daily, o.m. – morning, HR – heart rate, SpO2 - oxygen saturation, RR – pulse rate, BP – blood pressure.

thus the patient was in the transformation stage from moderate to severe phase. Since the breathing difficulty worsened without improvement in SpO2, the physician referred her to shift to the intensive care unit of Government tertiary health care hospital at Chennai. Due to severe mental stress and pandemic fear about COVID-19 deaths among hospitalized cases, the patient insisted not to move to the intensive care unit, so she was discharged against medical advice to return home at night.

7.2. Siddha treatment for SARS CoV-2

After reaching home at night on 25 May 2020, the family contacted our clinic and was given the *Vajra kandi maathirai* (VKM). Patient-1 started the first dose of VKM at night and gone to bed. Very next day morning, her body temperature has come down from 105 to 103° F, the SpO2 was elevated from 82% to 90%, and other symptoms (body pain, cough, and tiredness) were reduced to a

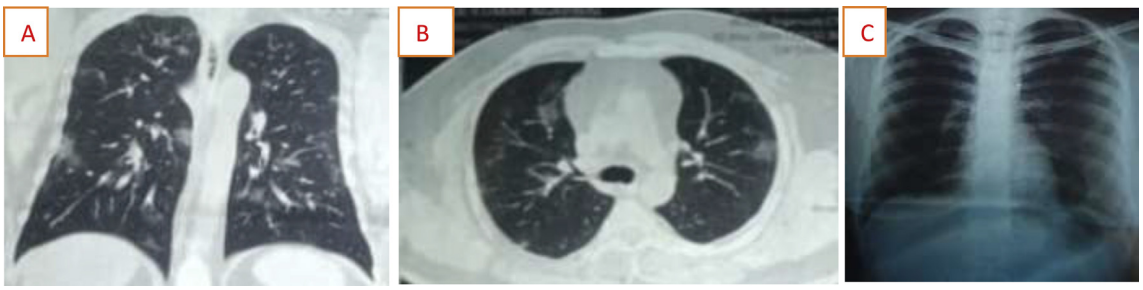

Fig. 1. CT- Chest of the father and X-ray chest of elder daughter. A, B) CT- Chest of the father showed multiple patches of ground-glass opacities in all the lobes of both the lungs and crazy paving pattern in right lower lobe with CT severity score of 11 (before treatment). C) The X-ray chest of elder daughter showed the subtle patchy opacities in the left lower zone (before treatment).

significant level. She consumed VKM thrice daily for first three days (T^{o} reduced from 105 to 102° F, SpO2 elevated from 82% to 100%), followed by twice daily for next two days (T^{o} 102 to 99° F, SpO2 maintained in 100%), then once a day for next two days (T^{o} 99 to 98.6° F, SpO2 maintained in 100%). Her other symptoms including cough have reduced gradually by 31 May 2020. She has consumed a total of 16 doses of VKM in 8 days (Table 1, Figs. 2 and 3).

For patient-2, VKM was given thrice daily for three days (26–28 May) followed by twice daily on 29 May. His temperature and all other symptoms were normalized with 11 doses for 4 days. Rest of the three patients consumed 9 doses of VC for a total of three days from 26–28 May (thrice daily) (Table 1). While taking VKM, the conventional therapy has been stopped.

8. Dietary practice during mercurial Siddha drug therapy [12]

The capsule is to be consumed with hot water or diluted honey with hot water. The patients were strictly advised to consume a recipe from/using any of the following; rice porridge, rice + milk porridge, wheat porridge, Idly, Idiyappam (string hoppers), green gram, tender drumstick, pepper, beans, dry mutton Meat/Jerked mutton meat, and Rain quail. Tamarind, sour tasty fruits/vegetables, alcohol, tobacco, bitter gourd, chicken, beef meat, fish should be avoided during the treatment. The diet restriction is usually advised to be continued for at least two more weeks from the last dose of VKM, this is called as *maru pathiyam*. The idea here is to avoid drug–food interactions, to get maximum efficacy, to favor mercury elimination from the body, and to restore or reverse the toxicity, if any; to achieve the desired efficacy safely.

9. Adverse effect monitoring

The patients were followed up through telephonic conversations weekly to observe any side effects. After the *maru pathiyam* (two weeks after the last dose of VKM with continuing dietary practices), the renal function, liver function and blood cells were evaluated.

10. Outcome of Siddha treatment

10.1. Safety of vajrakandi maathirai

There were no side effects reported by any of the patients and no abnormalities in blood parameters. Patient-2 had chronic kidney disease, with the pretexting elevated renal markers in the blood that remains the same even after the *vajrakandi maathirai* (Table 1).

10.2. Oxygen saturation

The SpO2 was elevated from 82% to 90% within one day after VKM therapy and subsequently it was maintained above 96%.

10.3. Fever and other symptoms

All patients have shown improvement in fever and other clinical symptoms satisfactorily. On 2 Jun 2020, the RT-PCR was repeated for all the five patients and the test results declared them Covid negative.

11. Follow up and patients' experience

All the cases were able to follow our instructions including dietary practices. They did not have any post covid complications for 6 months after the treatment. No adverse effects were observed. Patients were very happy for the cost effective treatment for COVID-19, without hospitalization.

11.1. Cost for the VKM anti-fever regimen

The cost of a single dose of VKM ranges from INR 15 to 50. In our case, the total expenditure for treating patient-1 (16 doses), patient-2 (11 doses), and others (9 doses each) was INR.800 (USD 11), INR.550 (USD 7.25) and INR.450 (USD 6) respectively (On 16 Jun 2020, USD 1 = INR 75.85). Moreover, it cut down the cost of hospitalization, oxygen administration or ventilator support and steroids administration to the father.

11.2. Chemical profile of vajrakandi maathirai

The *vajrakandi maathirai* was subjected for the chemical profiling using standard procedures of gas chromatography-mass spectrometry (ethyl acetate extract of VKM) for organic phytochemicals and inductively coupled plasma mass spectrometry for inorganics respectively [13,14].

It contains 22% mercury, 8.7% iron, and 1.3% arsenic along with 66 phytochemicals, among which 9-Octadecenoic acid-(E)- (21%), 1H-Imidazole, 4,5-dihydro-2-(phenylmethyl)- (21%) and 9,12-Octadecadienoic acid (Z,Z)- (21%) were the major compounds.

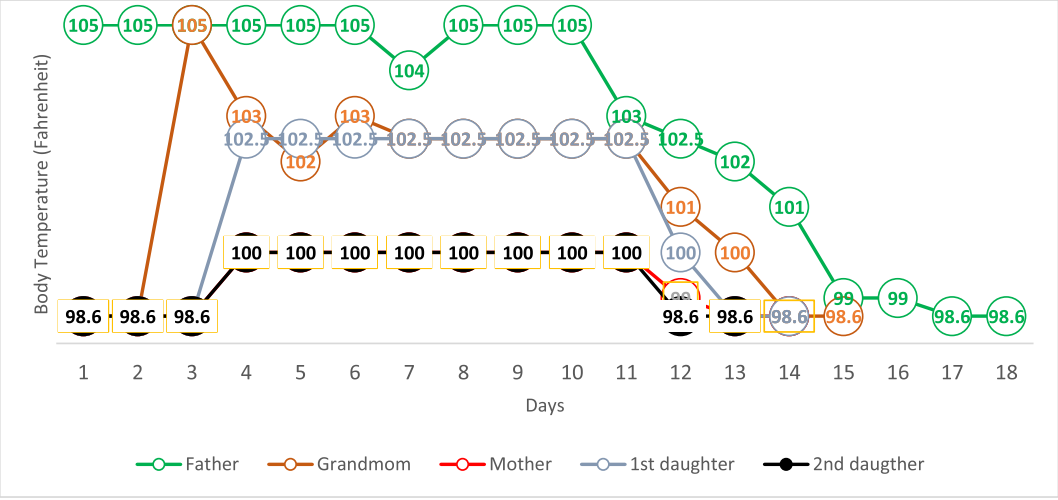

Fig. 2. The body temperature of all the 5 family members before and after Vajra kandi maathirai treatment.

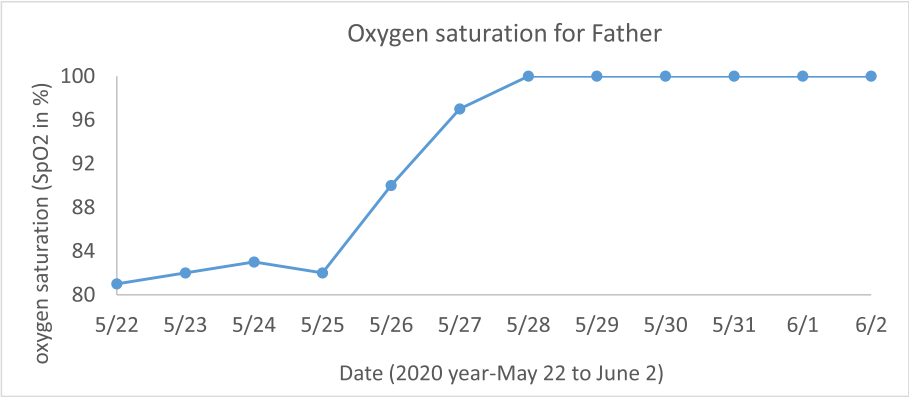

Fig. 3. Oxygen saturation level of the father before, during and after Vajra kandi maathirai treatment.

4-Epi-cubedol, Ledol, Longifolene, ylangene, Azulene, Methylprednisolone Acetate, Muurolene, Piperine, Tetradecanoic acid, Cyclic octaatomic sulfur, α-Copaene, and β-Sitosterol were some of the other compounds presented in this drug (Tables 2 and 3).

12. Discussion

In older editions (1952 publication) of British Pharmacopeia, the therapeutic use of mercurial drugs as diuretic and antibiotic has been included; but it was removed from the recent editions. Mercury and arsenic are the well-studied toxic agents and there is enough evidence for its toxic effects, hence its usage has been declined, even banned in many countries. On the other hand, certain traditional medical systems such as Siddha, Ayurveda, Tibetian Medicine, Traditional Chinese Medicine, and South African traditional medicine still include the mercury based formulations in their Pharmacopeia. Unfortunately, the beneficial side of mercury has not been addressed by the scientific community. In this paper, we reported the safe usage of a mercurial preparation *Vajra kandi maathirai* in five SARS CoV-2 infective patients.

The family comprises 5 members with a wide range of age groups (13–77 years), both male and females and the grandmother is 77 years old, with preexisting renal impairments and other comorbidities (hypertension and hypothyroidism). The clinical features are varying for each member, among them the father presented with moderate symptoms of SARS CoV-2 infection with SpO2 of 82% and CT severity score of 11 (ground-glass opacities in all the lobes of both the lung and Crazy paving pattern in right lower lobe).

VKM controlled the fever and other symptoms to all the 5 patients, and also improved the oxygen saturation significantly immediately with the first dose in patient-1. The duration of COVID symptoms during conventional therapy is 8–19 days [15,16]. In our cases, the duration of the symptoms is 8–12, in which first one week they were under conventional therapy that did not showed any improvement in symptoms, but the symptoms were relieved significantly with the VKM treatment. The duration could have been reduced in case VKM was used immediately after the first symptom.

It did not cause any toxicity to kidney or liver or hematological parameters. The low dose and shorter duration of therapy renders safe usage without acute toxicity. Siddha literature describes the use of this drug for short duration only, and not advised for long term therapy. This is the first clinical report of Siddha medicinal mercury as a safe therapeutic agent in SARS CoV-2 infective patients with mild to moderate symptoms. This may be the synergistic effect of all the phytochemicals too.

Vajra kandi maathirai is a combination of purified inorganics (mercury, arsenic, iron), marine product (Calcium shell of pearl oyster), cow milk and 17 herbs. There is a specific traditional pharmaceutical process to purify each of the inorganics, which include grinding with herbal juices and subjecting to heavy heat. After purification process, all were mixed together and filled in the capsule and distributed to patients. As per the Siddha literature, the duration of anti-fever regimen is twice or thrice daily for 3–8 days. The strength of this drug is short duration of treatment, no hospitalization is required and its cost effectiveness.

Aureolus Philippus Theophrastus also called Doctor Paracelsus, a Swiss physician worked with south Indian Siddha acharyas during 1515–1534 and learned and used similar mercury-based drugs during syphilis pandemic [17]. Constantine Joseph Beschi, also known as Vīramāmunivar, a Christian missionary from Italy reached India during 1710. He learned Siddha medical system from local practitioners and authored few books including *Sura manjari* (compilation on fever treatment) that describes many mercury and arsenic-based drugs against various types of severe-chronic fevers [18]. Siddha physician Nalla thambi Aasan, lived in the 18th century at Kanyakumari district of India had documented many such mercury and arsenic-based Siddha pills in his handwritten palm manuscript "*maaththirai alangaaram*" (Compilation of Siddha pills) [19]. Another Siddha physician Subramaniya Pillai who also lived in the 18th century at Kanyakumari district of India had also documented similar mercurial based drugs for acute severe fevers in his handwritten palm manuscript "*Sangara Chinthaamani*" (Siddha medical literature). In this literature, he also documented the side effects of mercury and its managements [20]. The Siddha term *soodha giranthi* denotes mercury-induced dermatitis (acrodynia), which reveals that the Siddha system had a deeper knowledge and experience in using mercury as a therapeutic agent as well as the management of its toxicities using specific herbal antidotes [21]. Considering these histories and literature, one could appreciate the extensive knowledge of Siddha system in using mercury as a therapeutic agent safely in the management of severe fevers.

Historically, Calomel (a mercurial salt, one of the ingredients of VKM) was used to treat yellow fever during its outbreak in Philadelphia in 1793 and also used in the treatment of syphilis. In the 18th and 19th centuries, the British doctors worked in India believed in local traditional medicine and also used Calomel for bilious fevers in a tropical environment, liver inflammation, and as a disinfectant. Later due to other better synthetic antibacterial agents, the use of mercury-based antibiotics became obsolete [22]. There is a separate hypothesis that due to the less solubility and high density, calomel

Table 2
GC−MS report of vajrakandi maathirai for phytochemical profile.

S.No.	Phytochemicals	Mol. formula	Mass	%
1	9-Octadecenoic acid, (E)-	C18H34O	282.3	2 1.16
2	1H-Imidazole, 4,5-dihydro-2-(phenylmethyl)-	C10H12N	160.1	2 0.62
3	9,12-Octadecadienoic acid (Z,Z)-	C18H32O	280.2	2 0.61
4	4-epi-cubedol	C15H26O	222.2	6.04
5	Naphthalene, 1,2,4a,5,8,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, [1S-(1.alpha.,4a.beta.,8a.alpha.)]-	C15H24	204.2	6.00
6	Ledol	C15H26O	222.2	4.44
7	Longifolene	C15H24	204.2	4.38
8	Longifolene-(V4)	C15H24	204.2	4.00
9	2-(3-Isopropyl-4-methyl-pent-3-en-1-ynyl)-2-methyl-cyclobutanone	C14H20O	204.2	3.51
10	2(3H)-Furanone, 3,4-bis(1,3-benzodioxol-5-ylmethyl)dihydro-, (3R-trans)-	C20H18O6	354.1	3.39
11	.alpha.-ylangene	C15H24	204.2	3.25
12	Azulene, 1,2,3,3a,4,5,6,7-octahydro-1,4-dimethyl-7-(1- methylethenyl)-, [1R-(1.alpha.,3a.beta.,4.alpha.,7.beta.)]-	C15H24	204.2	3.08
13	Naphthalene, 1,2,4a,5,8,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1.alpha.,4a.beta.,8a.alpha.)-(.+/−.)-	C15H24	204.2	2.88
14	Methylprednisolone Acetate	C24H32O6	416.2	2.65
15	7-Hexadecyn-1-ol	C16H30O	238.2	2.55
16	10-Hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14beicosahydropicene-2-carboxylic acid	C30H48O3	456.4	2.53
17	Tetradecanoic acid, 2-hydroxy-1,3-propanediyl ester	C31H60O5	512.4	2.50
18	1,3-Benzodioxole, 4-methoxy-6-(2-propenyl)-	C11H12O3	192.1	2.21
19	.gamma.-Muurolene	C15H24	204.2	2.20
20	2-Phenyl-2,4-octadienol	C14H18O	202.1	2.18
21	3-Hydroxymethyl-4-(1-hydroxy-2-methylprop-2-enyl)toluene	C12H16O2	192.1	2.09
22	Bicyclo [5.2.0]nonane, 2-methylene-4,8,8-trimethyl-4-vinyl-	C15H24	204.2	2.01
23	Piperine	C17H19NO3	285.1	1.96
24	Tetradecanoic acid	C14H28O2	228.2	1.77
25	Cyclopropa [16,17]pregn-4-ene-3,20-dione, 3′,16-dihydro-, (16.beta.)-	C22H30O2	326.2	1.67
26	.alpha.-Muurolene	C15H24	204.2	1.65
27	Benzene, 1,2,3-trimethoxy-5-(2-propenyl)-	C12H16O3	208.1	1.43
28	Cyclic octaatomic sulfur	S8	255.8	1.40
29	1,4,7,-Cycloundecatriene, 1,5,9,9-tetramethyl-, Z,Z,Z	C15H24	204.2	1.34
30	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	C10H12O3	180.1	1.25
31	Pyridine-3-carbonitrile, 1,2-dihydro-4-(3,4-dimethoxyphenyl)-6-(2-thienyl)-2-thioxo-	C18H14N2O2S2	354.1	1.24
32	Benzoic acid, 2-methoxy-, [1-amino-2-(2,4-dichlorophenoxy)ethylidenamino] ester	C16H14Cl2N2O4	368	1.17
33	.alfa.-Copaene	C15H24	204.2	1.08
34	.beta.-Sitosterol	C29H50O	414.4	1.06
35	Bicyclo [5.3.0]decane, 2-methylene-5-(1-methylvinyl)-8-methyl-	C15H24	204.2	1.02
36	n-Hexadecanoic acid	C16H32O2	256.2	1.01
37	gleenol	C15H26O	222.2	0.92
38	Ethyl iso-allocholate	C26H44O5	436.3	0.89
39	Benzene, 1,2,3-trimethoxy-5-(2-propenyl)-	C12H16O3	208.1	0.84
40	5,12d-Ethano (furo [2,3,4-mn]oxepino [2,3,4-ed]anthracen-2-on-9,12-diol)-, 6-methyl-2a,3,4,4a,5,6,7,8a-octahydro-	C21H24O5	356.2	0.78
41	1H-Cycloprop [e]azulene, 1a,2,3,4,4a,5,6,7b-octahydro-1,1,4,7- tetramethyl-, [1aR-(1a.alpha.,4.alpha.,4a.beta.,7b.alpha.)]-	C15H24	204.2	0.76
42	Thiazolo [3.2-a]benzimidazol-3(2H)-one, 2-(4-methylthiobenzylidene)-	C17H12N2OS2	324	0.75
43	Di-epi-.alpha.-cedrene	C15H24	204.2	0.70
44	Benzoic acid, 4-hydroxy-, hydrazide	C7H8N2O2	152.1	0.67
45	2-Hydroxy-4-isopropyl-7-methoxytropone	C11H14O3	194.1	0.67
46	Phenol, 2,6-dimethoxy-4-(2-propenyl)-	C11H14O3	194.1	0.66
47	Cyclohexane, 1-ethenyl-1-methyl-2-(1-methylethenyl)-4-(1-methylethylidene)-	C15H24	204.2	0.65
48	2,3,3′,4′-tetramethoxy-5-(3-methoxyprop-1-enly)stilbene	C22H26O5	370.2	0.65
49	Cubenol	C15H26O	222.2	0.64
50	Eucalyptol	C10H18O	154.1	0.63
51	Copaene	C15H24	204.2	0.60
52	2,4,6-Trimethoxyamphetamine	C12H19NO3	225.1	0.54
53	.alpha.-Guaiene	C15H24	204.2	0.51
54	Cyclohexanemethanol, 4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-, [1R-(1.alpha.,3.alpha.,4.beta.)]-	C15H26O	222.2	0.46
55	Apiol	C12H14O4	222.1	0.46
56	3-(Adamantan-2-yliden-methoxymethyl)-phenol	C18H22O2	270.2	0.46
57	Methyl 4,7,10,13-hexadecatetraenoate	C17H26O2	262.2	0.38
58	[4-(2,4-Dimethoxybenzyl)piperazin-1-yl]- (2-methoxyphenyl)methanone	C21H26N2O4	370.2	0.38
59	1,6-Octadien-3-ol, 3,7-dimethyl-, formate	C11H18O2	182.1	0.36
60	Terpinen-4-ol	C10H18O	154.1	0.36
61	2-Hydroxy-3-methoxybenzaldehyde, tert-butyldimethylsilyl ether	C14H22O3Si	266.1	0.36
62	(−)-Spathulenol	C15H24O	220.2	0.35
63	Humulane-1,6-dien-3-ol	C15H26O	222.2	0.34
64	3-Carene	C10H16	136.1	0.31
65	1H,3H-Furo [3,4-c]furan, 1,4-bis(3,4-dimethoxyphenyl)tetrahydro-, [1R-(1.alpha.,3a.alpha.,4.beta.,6a.alpha.)]-	C22H26O6	386.2	0.29
66	Dodecane, 1-fluoro-	C12H25F	188.2	0.28

Table 3
ICP-MS report of vajrakandi maathirai for inorganic profile.

S.No.	Elements	mg/kg	%
1	Mercury as Hg	222066.68	22.2
2	Iron Fe	86704.72	8.7
3	Potassium K	18311.45	1.8
4	Arsenic as As	13277.57	1.3
5	Calcium Ca	2345.94	<1
6	Sodium Na	2223.40	<1
7	Magnesium Mg	1299.33	<1
8	Phosphorus P	774.82	<1
9	Sulphur S	739.14	<1
10	Manganese Mn	384.98	<1
11	Aluminium Al	219.74	<1
12	Zinc Zn	146.81	<1
13	Strontium Sr	111.96	<1
14	Nickel Ni	33.25	<1
15	Chromium Cr	31.40	<1
16	Copper Cu	25.54	<1
17	Silver Ag	22.15	<1
18	Tin Sn	21.73	<1
19	Rubidium Rb	19.33	<1
20	Barium Ba	17.43	<1
21	Titanium Ti	10.15	<1
22	Lead Pb	2.64	<1
23	Scandium Sc	2.48	<1
24	Cobalt Co	2.23	<1
25	Vanadium V	1.45	<1
26	Antimony Sb	1.31	<1
27	Molybdenum Mo	1.20	<1
28	Tellurium Te	0.70	<1
29	Palladium Pd	0.34	<1
30	Bismuth Bi	0.20	<1
31	Gold Au	0.19	<1
32	Gallium Ga	0.18	<1
33	Selenium Se	0.17	<1
34	Tungsten W	0.16	<1
35	Niobium Nb	0.16	<1
36	Hafnium Hf	0.15	<1
37	Tantalum Ta	0.15	<1
38	Zirconium Zr	0.15	<1
39	Germanium Ge	0.13	<1
40	Caesium Cs	0.10	<1
41	Indium In	0.07	<1

gets insignificant absorption, rather it acts as a laxative and gets excreted out, so the possibilities for toxicity are less [23].

Cinnabar, one of the ingredients of VKM is chemically inert with a relatively low toxic potential when taken orally. In risk assessment, cinnabar is certainly less toxic than many other forms of mercury [24]. Earlier preclinical research on Siddha cinnabar drug has shown that the safe dose for human consumption is up to 112 mg/70 kg in man [25]. There are a number of other preclinical toxicological studies on Siddha mercurial preparations to show the safe dose range. The pharmacological actions of few Siddha mercury preparations have demonstrated their antipyretic, analgesic, anti-inflammatory, anticancer and antimicrobial activities [26–28]. Eliza et al. have published a clinical trial on 50 rheumatoid arthritis patients using Siddha mercury drugs without any side effects [29]. Government Siddha Medical College located at Palayamkottai and Chennai, India, have been using Siddha mercury drugs for cancers, psoriasis, and AIDS patients for the past 35 years without any adverse effects [30]. Thas et al. documented his experience of using Siddha mercury-based drugs for the management of chronic severe dermatological cases for the past 30 years without side effects [31]. Another interesting point to note is the long shelf life of 75 years as per the Siddha literature, which needs to be scientifically confirmed as it will be bneficial to have such stable drug [9].

Our earlier studies on Siddha mercury-based drugs showed interesting features such as nanosize of 20–80 nm and ensured safety in the *in-vitro* cytotoxicity assays as well as zebrafish toxicity models, that gave a novel scope for the therapeutic potential of Siddha mercurial preparations, which are different from the toxic mercurials [32]. Hence, it is understood that Siddha therapeutic mercurial preparations are possessing different properties from the laboratory mercury. VKM contains 22% mercury, 8.7% iron, and 1.3% arsenic along with 66 phytochemicals. Medicinal mercury and arsenic might have a broad spectrum activity against virus and inflammation, as these are the claims made by Siddha physicians. Future studies should be carried out to understand the mechanism of action of Siddha medicinal metals. Even though VKM contains mercury, it did not show any heavy metal toxicities in all the five cases and did not aggravate preexisting renal damage in the old age patient. The role of specific dietary practices during the mercury based drug therapy is yet to be understood. There is an urgent need for a detailed exploratory reverse pharmacological study on the therapeutic potential of this drug in COVID-19 cases.

13. Conclusion

Vajra kandi maathirai along with the specific dietary practice could be used to treat COVID-19 cases without side effects. The therapeutic benefit is a collective action of organics and phytocompounds. Rigorous research is required in larger population and also for drug discovery.

Authors contributions

All the authors have involved in planning, executing, and monitoring all the 5 cases. The case report was written by Arul Amuthan and edited as well as approved by all the other authors.

Funding

This study was not funded by any agencies.

Patient consent for publication

The informed consent from the adult patients and parents of the children and assent from the minor patient was obtained.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

We thank all the doctors and nurses who cared for these five patients. We thank Dr. Suresh Kumar (Consultant Infectious diseases) and Dr.S.Aarthy (Consultant Radiologist) of Apollo Specialty Hospital, Chennai, for the initial diagnosis, reporting of CT scan/X-ray and appropriate standard of allopathic care on time. We also thank Hubert Enviro Care Systems (P) Ltd, Chennai, India for performing ICP-MS and GC–MS chemical analysis for the Siddha drug.

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