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A Pharmacological Review of Siddha Classical Preparations for the Management of COVID-19 at TPEC COVID Care Centre, Vellore

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Authors' contributions

This work was carried out in collaboration among all authors. Author ST coordinates all components of the review paper and author KS has obtained and compiled the data. Author SS has the authority to support and initiate integrative management for COVID-19 patients and author PP is an advisor for all aspects of this analysis. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Despite the threat of coronavirus infection, the Siddha system of medicine, India's traditional medicine, plays an important role in southern India, particularly in Tamilnadu. It contributed considerably not only in the first wave of Covid-19, but also in the second wave. The Government of Tamilnadu developed Siddha COVID-19 treatment centers for asymptomatic, mild, and moderate COVID-19 positive patients in 2020. The TPEC COVID Care Centre initiated at Vellore also one of the Centers that can be managed by Siddha medicines and Siddhar's Yogam. As of July 14, 2021, about 4525 COVID positive patients had been treated with Siddha integrated treatment at Vellore alone in the first and second waves. *Kaba Sura Kudineer, Thalisathy*

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Vadagam, Amukkara Chooranam Mathirai, Bramanandha Bairavam Mathirai, and *Adathodai Manapagu* are indeed the five Siddha classical preparations used to manage the symptoms of COVID-19 positive patients at TPEC COVID Care Centre in Vellore. This Siddha medical practice is effective in conditions of symptoms and helps in the reduction of clinical outcomes. A pilot study at the same site confirmed the Siddha classical preparation's safety and effectiveness. A feedback analysis study performed at the same center also revealed that the above-mentioned Siddha classical preparations are beneficial in symptomatic treatment without causing any side effects. The medicines utilized in this study are typically proposed in other COVID care centers also in Tamilnadu. This review attempted to analyze the preclinical and clinical efficacy of Siddha Classical medicines used at that Centre for the management of COVID-19.

Keywords: Kaba Suram; Kaba Sura Kudineer; Siddha COVID Care Center; SARS-CoV2.

1. INTRODUCTION

The Ministry of AYUSH, Government of India recommended the guidelines for Siddha practitioners for COVID-19 on 2020. *Kaba Sura Kudineer, Thalisathy Vadagam, Amukkara Chooranam Mathirai, Bramanandha Bairavam Mathirai*, and *Adathodai Manapagu* are the recommended classical Siddha Preparations for asymptomatic to the moderate category of COVID-19 positive patients [1]. Before that recommendation, the Department of Indian Medicine and Homeopathy, Government of Tamil Nadu initiated Siddha COVID Care Centers in Tamil Nadu; TPEC COVID Care Centre at Vellore was initiated by the District Collector on July 9th 2020, with Siddha integrated approach. Here nearly 3800 positive cases were treated in both first and second wave with Siddha medicine and Siddhar's Yogam. As a result of this integrated approach on COVID-19, some Siddha formulations were analyzed in COVID care centers, which reported significant effectiveness and safety of Siddha formulations in asymptomatic, mild and moderate type of COVID-19 positive patients. This review is to explicate the scientific evidence that supports managing symptoms of COVID-19, immune-enhancing activity, and the formulations by Preclinical, Clinical, and ethno pharmacological analysis. In recent pasts, different therapeutic potentials of Siddha formulations, pharmacological activities of its ingredients, have been published in different international research journals. The present analysis is aimed to provide an updated review on recent research advancement of pharmacological activities, clinical evaluations of Siddha formulations.

2. METHODS

The bioactive chemical constituents, important pharmacological activities, and clinical efficacy of the Siddha formulations, and ingredients of the medicines which are used for the management of COVID-19 at TPEC COVID Care Centre, Vellore were analyzed. The clinical features of COVID-19 in the initial stage can be correlated with '*Kaba Suram'* in the pathology of disease as per Siddha literature [2]. Clinical characteristics like Fever, cough, chest discomfort, anorexia, dyspnea, and shortness of breath are commonly mentioned and those were observed in the COVID centers too. We have compiled a review on therapeutic potentials by collecting updated scientific research information from the internet. An attempt has been made to collect updated research information on Siddha formulations and their ingredients from the internet using Google search engine and Pub Med. The latest Clinical evaluations and Important Pharmacological activities of the Siddha formulations which were prescribed for the mild and moderate COVID-19 patients are summarized in Table-1. *Kaba Sura kudineer* -60 ml was prescribed twice a day, *Adathodai Manapagu* was given 10 ml twice daily with warm water after meals. *Amukkara Chooranam Mathirai,* 500 mg tablets were administered in the dosage of two tablets three times daily after meals. *Thalisathy vadagam Mathirai*, 500 mg Chewable tablets were given two tablets three times daily after meals. *Brammanandha Bairavam Mathirai*-100 mg tablets one (or) two pills administered two times daily after meals. All five formulations were administered for COVID-19 positive cases at TPEC COVID Care Centre Vellore until they recovered.

Table 1. Ingredients of Siddha Classical Preparations

S. No.	Name of the Formulation	Major Ingredient	Part Used	Pharmacological Activities of the Ingredients [3,4]	Clinical and Pre-Clinical studies of the Formulation
1.	***Kaba Sura Kudineer* (KSK)**	*Zingiber officinale*	Rhizome	• Anti-inflammatory effect • Antimicrobial Activities • Anti-asthmatic activity • Analgesic activity	• Significant (*P<0.05*) anti-inflammatory, antipyretic activity [5] • In acute toxicity study, there were no any adverse effects. In chronic toxicity studies (90days) in various dose level (0.15, 0.75, and 1.5 ml/kg B.wt) did not cause any changes in hematological and biochemical parameters with exception of a transient rise in uric acid, albumin, SGOT and lymphocyte level [6] • In silico molecular docking studies for the 37 phytoconstituents against the spike protein of SARS-CoV-2 (PDB ID: 6VSB) [7] • Obtained results from molecular docking showed that Acetoside, Luteolin 7 -rutinoside, rutin, Chebulagic acid, Syrigaresinol, Acanthoside, Violanthin, Andrographidine C, myricetin, Gingerenone -A, Tinosporinone, Geraniol, Nootkatone, Asarianin, and sitosterol are the main compounds from KSK plants which may inhibit COVID-19
		Piper longum	Fruit	• Immunomodulatory activity • Anti-microbial activity	
		Syzygium aromaticum	Flower bud	• Anti-pyretic effect • antiviral activity against Herpes Simplex virus	
		Anacyclus pyrethrum	Root	• Immuno-stimulating effect • Local anesthetic effect in vivo	
		Tragus involucrate	Root	• Analgesic activity using rat tail-flick method • Anti-inflammatory activity in carrageenan induced rat paw edema • Bronchodilator activity • Anti-inflammatory • Anti-pyretic activity on Brewer's yeast-induced pyrexia in rats	
		Barleria prionitis	Root	• Antipyretic activity	
		Terminalia chebula	fruit	• Antiviral activity and their protective activity against cytotoxic effects caused by influenza A virus	

		Justicia adathoda	leaves	• Anti-inflammatory activity by the modified hen's egg chrioallantoic membrane test • Bronchodilatory activity both in vitro and in vivo	giving a better energy score compared to synthetic drugs[8] • Retrospective cross-sectional data on 251 Positive COVID19 patients of both sexes irrespective of age recorded a reduces the Length of stay on average[9] • Among 50 participants in each group, by the sixth day, RT-PCR converted into negative for 27 patients, it showed *Kaba Sura Kudineer* was effective when compared with the control group against SARS-nCoV-2 patients[10] • KSK has immunomodulatory and thrombolytic properties in vitro models[11]
		Plectranthus ambonicus	leaves	• Analgesic • Antipyretic	
		Costus speciosus	Root	• Analgesic effect in acetic acid induced writhing and Eddy's hot plate models • Anti-inflammatory activity against carrageenan induced paw edema • Antipyretic activity by Brewer's yeast-induced pyrexia in rats	
		Tinospora cordifolia	Stem	• Immunomodulatory effect • Antiasthmatic activity in sensitized isolated guinea pig lung	
		Clerodendrum serratum	Root	• Anti-inflammatory activity in carrageenan induced paw edema and cotton pellet implantation methods • Anti-pyretic activity • Analgesic activity	
		Andrographis paniculata	Stem, Leaves	• Anti-inflammatory activity in carrageenan induced paw edema • Activity of andrographolide and its derivatives against influenza virus in vivo and in vitro	
		Cyperus rotundus	Root, tuber	• Anti-diarrhoeal activity in castor oil induced diarrhoea in mice • Anti-inflammatory activity • Analgesic activity	
		Cissampelos peraira	Root	• Antipyretic activity	
2.	***Adathodai Manapagu***	*Justicia adathoda*	Leaves	• Bronchodilatory activity both in vitro and in vivo [12] • potent SARS CoV-2 main protease inhibitors: an *in silico* perspective [13] • Antivirus activity that can inhibit viral attachment	• The combination of *Nilavembu Kudineer* and *Adathodai Manapagu* has shown a good response in high fever in the pediatric age group [14]

				and/or viral replication, and may be used for viral prevention [15] • vasicine shows the excellent antiviral property in Dock assay [16] • Anti-tussive effect on mechanical or chemical stimulation-induced cough [17]	• The synergistic effect of the Siddha add-on with standard treatment gave more promising results during the entire study period of COVID-19.
3.	***Thalisathy Vadagam***	*Abies Webbiana*	Leaves	• Benzenepropanol, 4-hydroxy-a-methyl, 2-furancarboxaldehyde, and 5-(hydroxymethyl) are the predominant components which having significant immunomodulatory and anti-inflammatory action [18] • Antitussive activity against sulfur dioxide-induced cough reflex [19] • Anti-pyretic activity [20] • Antibacterial activity [21]	There are no pre-clinical and clinical study data available for the complete formulation
		Piper nigrum	Fruit	• Anti-asthmatic activity In vitro [22] • Hepatoprotective Activity [23] • Immuno-stimulating Activity [24] • Anti-microbial activity [28]	
		Piper nigrum	Root	• Analgesic activity [25] • Anti-inflammatory activity [26] • Immuno-modulatory activity [27] • Inhibitory effect on monoamine oxidase and antidepressant-like activity [29] • Piperine has shown bioavailability enhancing effects on many therapeutically important drugs and nutrients[30]	
		Piper longum	Fruit	• Anti-asthmatic activity [31] • anti-inflammatory activity against carrageenan-induced paw edema [32] • Analgesic activity using rat tail-flick method and for NSAID type analgesia using acetic-acid writhing method [33]	

		• Immunomodulatory activity through suppression of proinflammatory cytokines [34] • Hepatoprotective effects against carbon tetrachloride-induced liver damage [35]
	Root	• Antifungal potential against Keratinophilic species [36] • Antimicrobial activity [37]
Zingiber officinale	Rhizome	• Anti-Inflammatory Effects [38] • Antiemetic effect of ginger [39] • Anti-avian influenza activity [40] • Anti-viral activity against the Chikungunya virus [41]
Cinnamomum zeylanica	Bark	• Anti-microbial activity [42] • Short-term germ-killing effect [43] • antibacterial activity against selected pathogens from Enterobacteriaceae [44]
Cinnamomum tamala	Leaves	• Immune modulatory activity [45] • Anti-diarrheal activity [46] • Anti-inflammatory activity in vivo and in vitro methods [47]
Mesua ferrea	Flower	• Analgesic activity [48] • Anti-microbial activity [49] • Antibacterial activity [50]
Elettaria cardamomum	Seed	• Anti-diarrheal activity [51] • Immuno-stimulant activity in doxorubicin treated rats [52]
Vetivera zizanoids	Root	• Anti-bacterial activity [53] • Anti-microbial activity [54]
Alpinia officinarum	Rhizome	• Anti-microbial activity [55] • Anti-cancer activity [56] • Inhibitory activity of pro-inflammatory mediators via inhibition of mitogen-activated protein kinase, p44/42, and transcription factor nuclear factor-kappa B [57]

4.	***Amukkara Chooranam Mathirai***	*Syzygium aromaticum*	Flower	• Anti-pyretic effect [58] • Antiviral activity against Herpes Simplex virus [59] • germicidal effect against various bacteria [60]	• Relieved morbidity and joint swelling [68] • Antioxidant and Anti-inflammatory Activities[69]
		Elettaria cardamomum	Seed	• Anti-diarrheal activity [51] • Immuno-stimulant activity in doxorubicin treated rats [52]	
		Piper longum	Fruit	• Anti-asthmatic activity [31] • anti-inflammatory activity against carrageenan-induced paw edema [32] • Analgesic activity using rat tail-flick method and for NSAID type analgesia using acetic-acid writhing method [33] • Immunomodulatory activity through suppression of proinflammatory cytokines [34] • Hepatoprotective effects against carbon tetrachloride-induced liver damage [35]	
		Piper nigrum	Fruit	• Anti-asthmatic activity In vitro [22] • Hepatoprotective Activity [23] • Immuno-stimulating Activity [24]	
		Zingiber officinale	Rhizome	• Anti-Inflammatory Effects [38] • Antiemetic effect of ginger [39] • Anti-influenza agents have been isolated from *Z. officinale*. TNF-α was reported as an anti-influenza cytokine [40] • Antimicrobial Activities of *M. avium and M. tuberculosis* in Vitro [41]	
		Withania somnifera	Root	• anti-inflammatory [61] • Anti-influenza Properties [62]	

				• anti-stress activity [63] • Antibacterial activity against Gram-positive isolates from pus samples [64]	
		Saccharum officinarum	Sugar	• Immuno-modulator [65] • Anti-inflammatory and analgesic effects [66] • Anti-platelet and Anti-thrombotic activity [67]	
5.	***Bramanandha Bairavam Mathirai***		Herbo-mineral formulation	• Analgesic • Anti-inflammatory • Antimicrobial Activities	• Anti-viral activity against CHIKV [70]

3. DISCUSSION

In developing countries increased cost of medicine, as well as their side effects, has become a great task when public health is concerned. Lack of effective therapeutics for most viral diseases, the emergence of antiviral drug resistance, high cost is the challenges in the treatment of viral infections. Investigations have been carried out from time to time to develop different types of polyherbal formulations to enhance the overall therapeutic potential of the formulation. And so, nowadays the traditional medical system and their herbal / herbo-mineral preparations are for various ailments becoming more popular. A lot of research articles confirm that this herb possesses effective anti-viral, anti-bacterial, and commonly antimicrobial activity without causing any hepatic damage and renal damage to a certain extent like conventional drugs.

As of July 14, 2021, Siddha treatment has helped to successfully treat 18,419 patients at 57 exclusive Siddha COVID-19 Care Centers (CCC) in Tamil Nadu, including four in the metro. Vellore has been handling the maximum number of positive cases, which over 4,525 patients treated.

The ingredients-based analysis of the Siddha formulations which were used in the TPEC COVID Care Centre at Vellore was having Anti-pyretic, Anti-viral, Anti-bacterial, Anti-asthmatic, anti-pyretic, anti-inflammatory, a bronchodilator, and immune-modulator effects. Medicines like *Kaba Sura kudineer* having a significant effect on SARS-CoV2 infection in both preclinical and clinical evaluations. *Thalisathy Vadagam* and *Amukkara chooranam Mathirai* having Anti-diarrheal activities.

Some of the important pre-clinical and Clinical studies of the Siddha Classical Medicines signify the effectiveness of COVID-19 management. In *Kaba Sura Kudineer*, In-silico molecular docking studies indicate 37 phytoconstituents have the potential to bind with SARS-CoV-2 Spike protein and 7 compounds may inhibit COVID-19 giving a better energy score compared to synthetic drugs and 1 RCT, prospective and 1 retrospective clinical trial exploring the evidence of the effectiveness of Siddha regimens on COVID-19 management. In *Adathodai Manapagu*, the synergistic effect of the Siddha add-on with standard treatment gave more promising results during the entire study period of COVID-19. These medicines are exploring the significant evidence to reduce the viral load, viral multiplication, and the severity of the infection.

The ingredients of *Thalisathy Vadagam*, *Amukkara Choorana Mathirai*, and *Bramanandha Bairavam Mathirai* having Anti-viral, Anti-inflammatory, Anti-asthmatic, anti-diarrheal, and analgesic activities, indicate the medicine having significant effect to manage the COVID-19 Symptoms like Cough, Sore throat, Fever, Headache, body ache. In the ingredients of *Amukkara Choorana Mathirai* having Anti-stress activity, it helps to reduce the depression during COVID-19 hospitalization. Asymptomatic, mild, and moderate covid positive patients have already been treated with the drugs discussed in this manuscript [71].

4. CONCLUSION

When comparing with the pharmacological aspects of this herb with Siddha literature strongly indicates the five classical Siddha formulations named *Kaba Sura Kudineer, Thalisathy Vadagam, Amukkara Mathirai, Bramanandha Bairavam Mathirai*, And *Adathodai Manapagu* can reveal Anti-viral, Anti-bacterial, Anti-asthmatic, antipyretic, anti-inflammatory, and bronchodilator with immune-modulatory effect and serve as a significant effect against Covid-19 management and post complications. While reviewing these medicines, they are having potential effectiveness on COVID-19 disease management. As per the recommendation from the Siddha Practitioner guidelines on COVID-19 [1], these medicines are having sufficient evidence to recommend to Covid-19 management.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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