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Fighting COVID-19: A Study to Compare Viable Treatment Options across Different Medical Systems

Review Article

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Abstract

During COVID-19, while many drugs from conventional medicine (CM) were falling short, those from Ayurveda, Siddha, Herbal Medicine, and Traditional Chinese Medicine (TCM) showed promising potential. The published recovery-aimed clinical studies on medicines from above-mentioned systems were retrieved. For CM, meta-analyses of studies using ICMR-protocol drugs, viz. hydroxychloroquine, azithromycin, favipiravir, ivermectin & remdesivir were searched. For other systems, preferably active-controlled, stand-alone studies, were considered. Their general characteristics, efficacy and safety outcomes were documented. The outcomes were evaluated on basis of a methodology inspired from 'WHO-Minimal common outcome measure set for COVID-19 clinical research'. The CM drugs were utilized either in multiple combinations or independently. Most studied combination was HCQ and azithromycin. HCQ efficacy was studied in biggest sample. These drugs did not exhibit significant efficacy for early clinical recovery and viral clearance. The adverse event (AE) incidences were also prominent. Barring TCM, studies using Ayurveda regime Tab. Immunofree and Cap. Regimmune and CVO+C, were done in only symptomatic patients. The efficacy of Tab. Immunofree- Cap. Regimmune regime was better than conventional care including azithromycin and favipiravir. The AE incidences in these studies were minimal. Medicines from alternative systems except CM exhibited better efficacy and safety in all outcome measures.

Keywords: Coronavirus, Herbal Medicine, Ayurveda, Chinese Medicine, Siddha.

Introduction

The surprises and threats introduced by COVID-19 pandemic, such as, the unavailability of a definite cure, were unique. (1) Till the pandemic waves settled, prevention by vaccination was considered as the best combat technique. However, great efforts were undertaken to find safe and effective cure for the same. (2). Worldwide, many conventional medicine (CM) interventions were repurposed and evaluated for their potential use. Various small- and large-scale clinical studies were undertaken. Limitations of these drugs were also revealed in many such studies. This further highlighted need to find better drug options for COVID-19 treatment from all available options.

Global data suggests that, the incidence of COVID-19, its severity and resultant mortality were notably lesser in countries where traditional medicines were incorporated in its preventive and curative management. (3) The recovery rate was also higher in these countries, especially in China and India. This was also observed in certain African countries that adopted 'Covid Organics'-an herbal medicine, from Madagascar.

In our present work, an overview of selected published clinical studies across different medical systems, viz., CM, Ayurveda, Siddha, Herbal medicine, and Traditional Chinese Medicine (TCM) has been carried out. The aim behind this was to understand efficacy of the drugs from these medicinal systems to fight COVID-19 and compare it with CM drugs. We have presented a succinct account of prominent, popular, and promising works in mainstream as well as complementary systems of medicine. Evidently, some of the complementary system remedies showed promise beyond pharmaceuticals. Despite this, there is no large-scale adoption of them in treatment protocols. We hope that this comparative study gives practitioners from all medicinal systems globally the tools to deal with similar situations, should the time demand. This will also facilitate large-scale adoption of the medicines from other systems in mainstream treatment protocols.

Materials and Methods

This narrative review was carried out in following stages. Relevant research articles were selected and studied.

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Literature search for published studies

The search strategies were different for interventions from CM and other complementary medicine systems. The data search was performed as follows.

Selection strategy for CM interventions

Globally, certain CM medicines formed the core of guidelines and directives for 'standard of care' or 'conventional care' (CC). Thus, robust data regarding their clinical studies in form of randomized controlled trials (RCTs), and their meta-analyses in available. For present review, CM drugs viz. hydroxychloroquine (HCQ), azithromycin, favipiravir, ivermectin and remdesivir were selected, as these were included in the ICMR and other global official guidelines for COVID-19 management at some point of time.

Selection strategy for interventions from other systems of medicine

The traditional systems such as Ayurveda, Siddha, Herbal medicine and TCM were utilised in COVID-19 management in specific parts of world. Several medicines were utilised by these systems too. However, most of them were used as adjuvants with CM drugs. To avoid possible confounding effect, we preferred for only such interventions which were used individually in CM-controlled clinical studies.

General search strategy

An extensive search was performed in the electronic databases, viz., SCOPUS, PubMed, DHARA, ProQuest, "National Repository on AYUSH COVID-19 Clinical and Other R&D Initiatives" (COVID-19 specific electronic database of AYUSH Research Portal (http://www.ayushportal.nic.in), and Google Scholar. Clinical studies published in English language between February 2020 and December 2022 were included in scrutiny.

For CM interventions, search terms such as, "COVID-19" or "SARS-CoV-2019" or "N-COV" or "Severe Acute Respiratory Syndrome Coronavirus" or "Coronavirus disease 2019" AND "Hydroxy chloroquine" or "Azithromycin" or "Favipiravir" or "Ivermectin" or "Remdesivir", AND "Systematic Review and Meta-analysis" were used. Only systematic reviews and meta-analyses were included for further consideration, irrespective of study designs of their component studies.

For other systems of medicine, search terms such as, "COVID-19 or "SARS-CoV-2019 or "N-COV" or "Severe Acute Respiratory Syndrome Coronavirus" or "Coronavirus disease 2019" AND "Ayurveda" or "Siddha Medicine" or "Herbal Medicine" or "Traditional Chinese Medicine", were used. After manual scrutiny, only prospective, clinical studies, systematic reviews, and meta-analyses were considered for further deliberation. Studies with stand-alone design were preferred. Retrospective analysis, non-pharmacological intervention studies, and observational studies were excluded.

Assessment strategy for selected studies

The assessment of selected studies was done on basis of a predefined set consisting of their efficacy and safety outcomes. This was inspired by 'Minimal common outcome measure set for COVID-19 clinical research' by WHO, viz., efficacy on viral burden, efficacy on clinical progression of disease and mortality. (4) The efficacy on viral burden was established by duration required for seronegativity in maximum number of patients as well as reduction in Cycle threshold (Ct) value. The efficacy on clinical progression was identified by attainment of symptomatic relief. Additionally, other efficacy outcomes, such as change in inflammatory markers, radiological findings etc., were also considered, wherever required. Mortality was studied as a safety outcome along with, adverse events (AE) and adverse drug reactions (ADR).

Results

Representative systematic review and meta-analysis for each of the drugs, viz., HCQ, azithromycin, favipiravir, ivermectin and remdesivir, were selected for reviewing CM contribution. These selected studies were composed of multi-arm RCTs, with independent as well as combination use of these drugs.

Next, assessment of these interventions was carried out according to pre-defined efficacy and safety outcome measures. The general characteristics of selected CM intervention studies and their assessment is mentioned in Table 1.

Various allopathic drugs and therapies were empirically used for COVID-19 management since its outbreak. However, all of these were subsequently tested in RCTs and this data was published. HCQ and azithromycin combination was utilised in many studies. As expected, the sample sizes studied were quite large, with highest patient number including the meta-analysis to study HCQ efficacy. Barring remdesivir, these drugs were studied in multiple combinations along with independent usage. Further, we studied the major efficacy and safety outcomes reported by these studies.

In the next stage of study, we retrieved interventions from other systems of medicine, viz., Ayurveda, Siddha, Herbal Medicine and TCM. As mentioned in search strategy, prospective clinical studies with active-controlled, stand-alone design were preferably retrieved. In addition to three such studies from Ayurveda, we included a placebo controlled stand-alone study utilising a famous Ayurveda P & P intervention, Coronil. The popular herbal medicine, Madagascar remedy COVID ORGANICS, viz., CVO+C was selected. However, due to unavailability of its active-controlled trial, the placebo-controlled study was selected. Our search revealed that, TCM management protocol for COVID-19 consisted of drugs, viz., Chinese medicine formulas (*Qingfei Paidu* decoction, *Huashi Baidu* formula, and *Xuanfei Baidu* formula), Chinese patented medicines (*Jinhua Qinggan* granule and *Lianhua Qingwen* capsule), and Chinese medicine injections (*Xuebijing* and *Xiyanping* injections). These drugs were utilised as integrative therapy along with prevalent CC drugs. Thus, their representative meta-analysis was selected for further review.The general characteristics of these selected studies are presented in Table 2.

Table 1: General Characteristics and Assessment of Selected Studies utilizing CM Interventions

Intervention	Study	No. of studies & (No. of patients) included in meta-analysis	COVID-19 gradation of Study Population	Intervention Arms	Efficacy outcomes	Safety outcomes
HCQ	Kashour *et al (5)*	21 (20,979)	Asymptomatic, Mild, Moderate and Severe	-HCQ -HCQ/ Chloroquine -HCQ + Azithromycin	There was no association between HCQ and viral clearance, risk of hospitalization and, reduction in requirement of intensive care.	No significant association between HCQ and mortality. Evidences of toxicity due to chloroquine and HCQ observed.
Azithromycin	Mangkuliguna *et al (6)*	17 (19,189)	Asymptomatic, Mild, Moderate and Severe	- Azithromycin - Azithromycin + HCQ	No significant association with clinical improvement, reduction in hospitalization and requirement of intensive care.	Lower mortality observed, however, it was statistically insignificant. Relatively safe in terms of adverse effects reported.
Favipiravir	Hassanipour *et al (7)*	9 (827)	Mild, Moderate	-Favipiravir -Favipiravir + Interferon-a -Favipiravir + Interferon-beta-1b -Favipiravir + CC	There was significant clinical improvement in 7 days in Favipiravir group patients. The viral clearance was observed after more than 14 days in them, which was insignificant as compared to control group.	There was no significant effect on mortality. Mild to moderate AEs such as nausea, vomiting, diarrhoea, chest pain, and increased levels of serum liver transaminase and uric acid were observed.
Ivermectin	Deng *et al (8)*	17 (2,697)	Asymptomatic, Mild, Moderate and Severe	-Ivermectin -Ivermectin + Doxycycline - Ivermectin + CC - Ivermectin + HCQ	No significant reduction in duration for viral clearance as well as hospitalization.	There was no reduction in mortality. It can be considered safe, due to no association with increase in AE incidences.
Remdesivir	Abdouh *et al (9)*	4 (7334)	Hospitalized moderate and severe	-Remdesivir	No significant association with early clinical improvement, however rate of recovery was higher.	No significant effect on increase in mortality and serious AEs.

Table 2: General characteristics of selected Ayurveda, Siddha, Herbal Medicine and TCM studies

Study	Study Interventions	Sample size	Study Population Age	COVID-19 gradation of Study Population	Components of control group	Treatment Duration
Ayurveda						
Kamat *et al* (10)	Tab. Immunofree and Cap. Regimmune	100	18-70 years	Mild, Moderate	CC (Tab. Paracetamol, Tab. B Complex, Vitamin C, Tab. Cetrizine, Tab. Pantoprazole, Azithromycin, and Favipiravir)	10 days
Rais *et al* (11)	*1)Vyaghryadi Kashaya* + *Pippali* powder 2) *Samshamani Vati* +*Shunthi* powder+ *Rasona Kalka*	120	25-60 years	Asymptomatic and mildly symptomatic	CC (Vitamin C, Tab. Paracetamol)	10 days
Shukla *et al* (12)	*Guduchi Ghana Vati*	30	≥18 years	Asymptomatic, Mild, Moderate	CC (HCQ, Vitamin C, Tab. Paracetamol, Multivitamins, Zinc)	10 days
Devpura *et al* (13)	Coronil	100	15-80 years	Asymptomatic, Mild	Placebo	7 days

Siddha						
Nataraja n *et al* (14)	*Kabasura Kudineer*	60	18-55 years	Asymptomatic	CC (Vitamin C, Zinc)	7 days
Herbal Medicine						
Rakotos aona *et al* (15)	CVO+C (Covid Organics)	276	≥18 years	Mild, Moderate	Placebo	15 days
Traditional Chinese Medicine						
Wang *et al* (16)	*Qingfei Paidu* decoction, *Huashi Baidu* formula, *Xuanfei Baidu* formula, *Jinhua Qinggan* granule, *Lianhua Qingwen* capsule, *Xuebijing* injection, *Xiyanping* injection	2222 (25 studies)	18-85 years	Mild, Moderate, Severe	CC (As per guidelines)	7-21 days

Further, we reviewed them based on the efficacy and safety outcomes as mentioned in the methodology section. A review of these outcomes is presented in Table 3.

Table 3: Efficacy and safety outcomes of selected Ayurveda, Siddha, Herbal Medicine and TCM studies

Study	Efficacy Outcomes			Other Efficacy Outcomes	Safety Outcomes (AE/ADR)
	Effect on Viral Burden (seronegativity)	Effect on Clinical Progression (Symptomatic relief)	Mortality		
Ayurveda					
Kamat *et al (10)*	Seronegativity by Day 5- Study group -88 % Control group- 72 % Seronegativity by Day 10- Study group -100 % Control group- 88 % (Statistically significant difference between study group and control group)	Study group- Symptomatic relief in 88 % patients by Day 5 and 100 % patients by Day 10 Control group- Symptomatic relief in 72 % patients by Day 5 and 100 % patients by Day 10 (Statistically significant early relief in study group)	Nil	Improvement in chest radiograph in study group on Day 5 was seen in 80 % patients and 96% on Day 10. In control group, 70 % patients showed such improvement on Day 5 and 88 % on Day 10. This difference was statistically insignificant when compared within group and between groups. The decrease in levels of C-Reactive Protein and Procalcitonin were significant within study group as well as control group. However, insignificant when both groups were compared. There was significant increase in SpO_2 in study group. However, such increase was insignificant in control group or when both groups were compared. There were no significant or off-limit changes in CBC, ESR and other biochemical tests such as, Serum Sodium, Serum Potassium, BUN, AST, ALT, Serum Creatinine and ALP The improvement in ECG was seen in 76.9 % patients in study group and 65.2 % patients in control group, on Day 10. The improvement in study group was statistically significant. On telephonic follow-up on Day 21, the patients from both groups were reported as healthy.	Study group- Mouth ulcers in one patient-self- resolved Control group- Vertigo and nausea & vomiting in two patients each, dizziness, drowsiness, and mouth ulcers in one patient each- self-resolved

Rais *et al (11)*	Seronegativity by Day 5- Study group A-92.5% Study group B-87.5 % Control group- 57.75% Seronegativity by Day 7- Study group A-100 % Study group B-97.5 % Control group- 72.75% Seronegativity by Day 10- Study group A-100 % Study group B-100 % Control group- 90% (Statistically significant difference between study group A & control group as well as study group B & control group)	Least progression of symptoms in study groups A & B, in comparison with control group. Study group A- Statistically significant relief from fever, cough, sore throat, and irritability, when compared with study group B & control group Study group B- Statistically insignificant improvement in abnormal sensation of taste and general weakness, when compared with study group A & control group	Nil	None	Study group A- Loose stools with mild weakness in two patients- recovered after medication Study group B- mild burning sensation in abdomen in three patients- recovered after medication Control group- One SAE- hospitalization due to severe dyspnea
Shukla *et al (12)*	Seronegativity by Day 5- Study group -66.6 % Control group- 53.3% Seronegativity by Day 10- Study group -93.3% Control group- 66.6% (Statistically insignificant difference between study group and control group)	Study group- Symptomatic relief in all patients, except one, by Day 5 Control group- Symptomatic relief in all patients by Day 5 (Statistically insignificant difference between study group and control group)	Nil	Normal vital parameters in both groups Significant reduction in IL-6 levels in both groups compared to baseline Significant increase in IgG levels by Day 10 in control group Significant decrease in IgM levels by Day 10 in study group	None reported in both groups
Devpura *et al (13)*	Seronegativity by Day 3- 71.1% patients in study group and 50 % patients in placebo group. This difference was statistically significant. -Seronegativity by Day 7- 100 % patients in study group and 60% in placebo group.	Not Assessed	None	Better reduction in the serum hs-CRP and IL-6 and TNF-α levels	None observed
Siddha					
Natarajan *et al (14)*	The viral load declined significantly as evident from decrease in Ct value, in both groups -The decrease in Ct value was more pronounced in in study group.	Patients in both groups remained asymptomatic during study duration	None	The serum levels of biomarkers such as IFNγ, TNF-α and IL-6 remained within normal limits in both groups.	None observed
Herbal Medicine					
Rakotoson *et al (15)*	Seronegativity by attained by 42.42%, 70.45%, 76.52%, and 89.39% patients from study group on Day 7, 14, 21 and 28 respectively. -In control group, it was 27.08%, 39.85%, 40.97%, 56.94%, and 77.78% -The early seronegativity in study group was statistically significant	Not assessed None of the patients in study group progressed to severe stage.	None	No marked difference in hematological parameters, liver function tests and renal function tests in both groups	Study group- severe asthenia, dyspnoea, digestive disturbances Control group- Dyspnoea, cardiac disturbance, digestive disturbances
Traditional Chinese Medicine					
Wang *et al (16)*	No favourable effect of study drugs on seronegativity, compared with control group	Moderate efficacy exhibited by study drugs in early clinical improvement.	Reduced mortality in study group patients observed	Suggestive evidences on efficient decrease in inflammatory cytokines.	No significant difference in AE incidences in both groups

Ayurveda

A variety of Ayurveda medicines were studied for preventive as well as curative management of COVID-19. Not only classical but, some patent and proprietary (P & P) drugs were utilised. Our search revealed that only three studies were carried out using a stand-alone design and CC as comparator. Thus, they were included. Also, Coronil, a well-known P & P formulation regime was included, in spite of being a placebo-controlled study.

Tab. Immunofree and Cap. Regimmune- In this study carried out in 100 mild and moderately symptomatic COVID-19 patients, 88 % became seronegative and reported symptomatic relief by day 5 and 100 % by day 10 in study group. Both these outcomes were statistically significant in inter-group comparison. The study regime also showed improvement in chest radiograph. On Day 10, 96 % patients in study group showed this improvement compared to 88 % in control group. There was also marked decrease C - reactive protein and Procalcitonin levels and increase in SpO2 in study group patients. The improvement in ECG was seen in 76.9 % patients in study group and 65.2 % patients in control group, on Day 10. The improvement in study group was statistically significant. Minor self-resolving AE, mouth ulcers was reported in one patient of study group. However, AEs, viz., vertigo, nausea & vomiting, dizziness, drowsiness, and mouth ulcers were reported in some control group patients.

Vyaghryadi Kashaya + Pippali powder and *Samshamani Vati + Shunthi* powder+ *Rasona Kalka*- This study by Rais *et al* was a three-arm study, where simultaneously, two drug regimens were independently compared to the CC in 120 asymptomatic and mildly symptomatic COVID-19 patients. Patients receiving *Vyaghryadi Kashaya + Pippali* powder study regimen became seronegative by Day 7, as compared to Day 10 for those receiving other study regiment. Least progression of symptoms was observed in both study groups than the control group. Patients receiving *Vyaghryadi Kashaya + Pippali* powder study had statistically significant relief from fever, cough, sore throat, and irritability, when compared with other study group & control group. Patients receiving study interventions reported minor AEs such as, loose stools with mild weakness, and mild burning sensation in abdomen. However, a patient from control group was hospitalised due to severe dyspnea.

Guduchi Ghana Vati- This study was carried out in 30 asymptomatic, mild, and moderately symptomatic COVID-19 patients. 93.3 % patients from study group achieved seronegativity by Day 10, as compared to 66.66 % from control group. All but one patient from study group exhibited symptomatic relief by day 5 itself. Both groups also exhibited reduction in IL-6 levels. No AEs were reported.

Coronil- The Ayurvedic P & P medicine, Coronil, was tested among 100 asymptomatic and mildly symptomatic COVID-19 patients in a placebo-controlled study. By Day 7, clinical recovery as well as seronegativity were observed in the study group patients. There were no AEs reported.

Siddha

Kabasura Kudineer- In the study carried out among 60 asymptomatic COVID-19 patients, decrease in viral load (expressed from declined Ct value) was observed in both groups by Day 7, with marked decrease in the group treated with *Kabasura Kudineer*, a polyherbal Siddha formulation. None of the patients progressed to symptomatic stage. No AEs were reported.

Herbal Medicine

CVO+C- This medicine contains two herbal origin compounds derived from *Artemisia annua* and *Cinnamomum camphora*. A placebo-controlled study was carried out to assess its efficacy in 339 mild to moderately symptomatic COVID-19 patients. It was found to be effective in 87.1% patients. Total recovery was observed by Day 14 in 70.45% patients.

Traditional Chinese Medicine (TCM)

A systematic review and meta-analysis of 25 studies involving 2222 mild and moderately symptomatic COVID-19 patients revealed that, no significant role of TCM medicine addition in attaining early seronegaticity. However, they were useful in reducing disease symptoms. They were also capable in greatly reducing the inflammatory biomarker levels. Good safety and lower mortality were also reported.

Discussion

The review of selected studies carried out in curative COVID-19 management across CM drugs to natural medicines from the Ayurveda, Siddha, herbalist traditions, and TCM provided certain important perspectives. Our review suggested that the natural medicine systems have depicted good efficacy by reducing viral burden and aiding early symptomatic relief. On the other hand, efficacy of certain CM drugs was unimpressive.

We selected only RCTs and meta-analyses in this review, due to their higher grade of evidence. (17) Also, active-controlled studies were preferred over placebo-controlled studies. Our initial observation revealed that, most of the studies were using an add-on design, where study interventions were used as adjuvant to CC. It was thought that, the stand-alone intervention studies could possibly nullify this confounding effect of CC given along with study drug. Thus, by far possible, only such studies were included.

The review of studies utilising allopathic drugs, viz., HCQ, azithromycin, favipiravir, ivermectin and remdesivir was done. As these drugs were a part of CC at certain times, meta-analyses were only included, for reviewing outcomes reported by many RCTs. None of these studies strongly upheld their efficacy claims for early recovery and other outcomes. Notably, current ICMR guidelines for COVID-19 management have barred usage of HCQ, Azithromycin, Favipiravir, and

Ivermectin. (18) This further sustains the need to put forward potentially useful contenders from other systems of medicine.

The studies from other medical systems were carried out in asymptomatic, mildly positive, and moderately positive COVID-19 patients. The exclusion of severely ill patients in most of these can be understood, though. Considering the bewildered status of allopathy and 'alternate and complementary' status of other natural medicines, it would have been difficult to receive even ethical clearance to carry such stand-alone studies among severe cases. Nonetheless, their contribution is valuable considering the fact that most patients belonged to these categories than the severe. (19)

In India, in addition to allopathic interventions, traditional AYUSH (Ayurveda, Yoga, Unani, Siddha and Homeopathy) interventions were also used. They were explored to boost innate immunity and even manage recovery from COVID-19 infection. (20) Our previous research had elaborated that; 197 such studies were registered in Clinical Trials registry-India (CTRI). (21) Notably, the Ayurveda medicine regime of Tab. Immunofree and Cap. Regimmune studied by Kamat *et al* included only symptomatic COVID-19 patients, in contrast to other two studies in this category. This consideration probably helped in better understanding of symptomatic relief, as their data was not diluted with already asymptomatic patients. This study also had a broader inclusion criterion of patients up to 70 years. Given that the study was conducted in three different hospitals, the patient diaspora was also extensive. Notably, Tab. Immunofree and Cap. Regimmune regime provided quicker symptomatic relief and seronegativity than the CM drugs used in control group. Apart from usual two-arm design, there was a three-arm study by Rais *et al*. The usage of two study arms and one control arm was a clever attempt to utilize same study setup to evaluate efficacy of more than one regime. Although this was not an adaptive design like the WHO-Solidarity trial, such efforts will be more helpful in conducting time and cost-efficient, yet outcome-focused clinical studies. While interventions used by Rais *et al* and Shukla *et al* were purely classic, those used by Kamat *et al* were exceptionally different. Regimen of combination of one ayurveda proprietary drug and one nutraceutical was noteworthy. It is comparable to the composite drugs regimen used by TCM experts. The Ayurveda proprietary formulation, Immunofree, had a diverse ingredient range. It encompassed ingredients such as, anti-parasitic agents (E.g., *Kalmegh*) (22), anti-viral agents (E.g., *Haridra*) (23), anti-microbial agents (E.g., *Tulasi*) (24), anti-coagulation agents (E.g., *Kumari*) (25), immunomodulatory agents (E.g., *Guduchi*) (26), antipyretics (E.g., *Pippali)* (27) and so on. The symptomatic relief, which also implies inverse of disease progression was substantially observed in these studies. It would have initiated some fantastic results, if these studies were carried out in large sample size. Even the effects on achieving seronegativity were promising in these studies. As against very slow viral clearance ability of CC drugs, the Ayurveda interventions were quite effective.

Various Siddha medicines, such as *Kabasura Kudineer, Nilavembu Kudineer, Adathodai Manapagu* etc. were utilized in curative COVID-19 management. However, as *Kabasura Kudineer* was the most studied of these, it was selected for present review. Only one study could be found where, *Kabasura Kudineer* was used as a stand-alone single medicine with CC as comparator. Thus, only that study was included, which was carried out in asymptomatic COVID-19 patients. The marked decrease in viral burden reported in this study needs to be also ascertained in symptomatic patients.

Herbal medicine systems, such as African medicine was also actively involved in the COVID-19 management. 'CVO+C,' popular as 'Covid-Organics' or 'Madagascar remedy,' is a traditional medication developed and promoted by government of Madagascar. It was successfully used across many countries in successfully treating COVID-19. Its main content, '*Artemisia annua*,' has exhibited in-vitro inhibitory activity on coronavirus. (28) Interestingly, this herb known as '*Damanaka'* in Ayurveda, was also present in Tab. Immunofree.

The Chinese national health commission mandated the use of TCM with standard care treatment for all COVID-19 patients. (29) It was believed that using TCM protocol was instrumental in controlling the COVID-19 outbreak there. The evidence generation regarding the preventive and curative efficacy of before-mentioned TCM drugs is impressive. Inclusion of severe patients was a notable fact regarding these studies. However, most of the studies were integrated in nature with TCM used as adjuvant to CC.

Our study had certain limitations due to potential bias in study selection. We tried to avoid such methodological shortcomings by including RCTs and systematic reviews only. However, due to diverse nature of systems studied, it could not be completely achieved. Also, the sample sizes for some studies included were quite small. Still, they were included owing to their conspicuous contribution.

Although the availability of evidence for CM interventions is robust, it does not promote their superior efficacy. On the other hand, we cannot dismiss the scale of efficacy exhibited by studied utilizing interventions from other systems of medicine. Along with marginal efficacy, threats of AEs of various severities were associated with most of the drugs from CM. A range of adverse effects of the CC drugs such as, vitamin-D, zinc, remdesivir, hydroxychloroquine and chloroquine, azithromycin, dexamethasone, amantadine, and aspirin etc. have already been reported. (30) The AEs from the reviewed studies from other systems of medicines were mostly of mild and self-resolving nature. This aspect certainly puts them in a positive light. A convincing safety and efficacy data is considered as an important issue to focus for believers of science and evidence. (31) Such promising potential exhibited by traditional medicine interventions in dire situations of COVID-19 are surely assuring, as per the

published data. We also wish to point out the need to devise a methodology to evaluate efficacy of different medicinal systems among populations diverse in terms of ethnicity, genetic makeup, geographical distribution etc. As mentioned by Walach *et al*, utilising multiple methods and study designs as well as counterbalancing their strengths and weaknesses will be helpful for future researchers. (32)

Conclusion

Seeking effective COVID-19 treatment was of principal importance during the pandemic, by exploring all possible options. Once highly revered CC drugs like HCOQ, azithromycin, favipiravir, etc. were deemed of little use in long course, where other 'complementary' medicine systems showed potential use. However, large studies with more scientific rigor and outcome dissemination in good quality publications was a conspicuous shortfall for these other medical systems. Also, more efforts by global policy-makers would have been appreciated to incorporate natural remedies for treatment of COVID-19. Nevertheless, this lesson learnt can prove useful should similar situation develops in future.

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