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A REVIEW ON EVIDENCE-BASED CLINICAL RESEARCH IN TRADITIONAL MEDICINE FOR COMBAT COVID-19

J. I. D. Diddeniya and P. K. Perera *

Institute of Indigenous Medicine, University of Colombo, Colombo, Sri Lanka.

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Correspondence to Author:
P. K. Perera

Institute of Indigenous Medicine, University of Colombo, Colombo, Sri Lanka.

E-mail: kamalperera@iim.cmb.ac.lk

ABSTRACT: Covid-19, caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is a life-threatening disease that has been declared a global pandemic. Even with the intervention of numerous medical systems to combat Covid-19, an effective remedy is not yet in sight rather than supportive therapies accompanied with anti-viral drugs and vaccines. The usage of these medicines has caused for unexpected side effects, and at present, various mutant forms of this virus have been identified from different countries. Hence, the necessity of an effective treatment regimen is highly expected. The attention direct towards Traditional Medicine (TM) is increasing day by day as it is well known for immune modulation. Therefore, this review was conducted with the aim of systematically reviewing the relevant literature of TM based on clinical studies conducted on Covid-19 patients and provides a summary on the evidence-based potential use of TM in the treatment of Covid-19. This review was conducted by using the databases; Science direct and PubMed for studies published from 1st of December 2019 to 1st of February 2021. In order to obtain further data, a manual search was also carried out. After scrutinizing all the articles, there were 29 total articles included in this present review. The evidence suggested that TM could regulate immunity and gives anti-viral, anti-inflammatory effects along with disease management and prevention. However, if these treatment modalities have any public health implications, further randomized controlled trials in humans will be needed.

INTRODUCTION: At present, the global community is facing a previously inexperienced pandemic of novel coronavirus disease (Covid-19) caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) [1]. According to the World Health Organization (WHO) definition, a pandemic means an epidemic that occurs worldwide or over a very wide area crossing boundaries of several countries and usually affecting a large number of people [2]. Due to its severity and rapid spread worldwide, it has been declared a pandemic by WHO.

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Therefore, this is considered a World health Emergency. As the virus, SARS-CoV-2 was first identified in Wuhan city of China, most scientists believed it has been originated in China. Studies have shown that this pandemic which is highly infectious and contagious, has originated in connection to a seafood market in Wuhan. Still, a team of Chinese researchers said that there were two types of this virus circulating in Wuhan and only one is associated with the market [3].

Recently, a team of Scientists who led a mission in China by visiting there stated that the "jump" from bats to humans likely involved an intermediate host such as ferrets, rabbits, or bamboo rats susceptible to the virus and sold at the Wuhan market [4]. The disease has spread all over the world, with more than 181,190,692 confirmed cases and 3, 925, 285 deaths as of June 26, 2021 [5]. The facts such as age above sixty-five years and co-morbidities like

chronic lung disease, liver diseases, chronic kidney disease, diabetes mellitus and cardiac ailments have been identified as the facts which increase the mortality rate [6]. It can be transmitted either from symptomatic or asymptomatic by contact, droplets, and fomites [7] and in symptomatic cases, patients present with fever, sore throat, cough, pneumonia, fatigue, headache, diarrhea and dyspnea [8]. Impaired immunity plays a major role in the pathogenesis of this disease. Recently it was found that, even though Covid-19 is a respiratory illness, it also affects to body's primary organs such as the heart, liver, brain and kidneys [9].

As a result, the severity of the disease worsens day by day. Not only that, but multiple new mutant variants of this virus have also been identified from the countries including United Kingdom, Japan, South Africa and America, *etc.* [10]. By now, several vaccines have been tested positively answering Covid-19, but the new cases of Covid-19 reported worldwide have not yet been reduced in a considerable value. And not only that, some cases have been reported from many countries where there are unfavorable side effects of the vaccination resulted after receiving it.

To date, no specific antiviral treatment has proven effective even though vaccination has been given to people for those who are seeking immunity enhancement. It will take a few more years to make a specific antiviral treatment against Covid-19; hence, infected people rely on symptomatic treatment and supportive care during their hospital stay. Despite the efforts made to combat this virus SARS-CoV-2, the pandemic is continuing to spread worldwide. It implies the necessity of clinically proven therapeutic management. As TM has an immune-modulatory effect, it plays a significant role in the prevention and treatment of Covid-19 [11]. These Traditional Medicinal preparations are known to have a potential capacity to modulate the immune response. Therefore the attention of the community has been drawn towards the TM in a significant manner.

Therefore, it is essential to search and review the evidence-based clinical research in TM for combat COVID-19 as its usage has become most popular among the community at present and this research was aimed at that.

MATERIALS AND METHODS:

Study Design: A review method was applied by making use of clinical studies which have been conducted only on human beings.

Data Collection: Research papers published regarding Traditional Medicine including Traditional Chinese Medicine (TCM), Indian Traditional Medicine (Ayurveda), Sri Lankan Traditional Medicine in combat Covid-19.

Sources: WHO Covid-19 research database, PubMed, Science direct, International Clinical Trials Registry Platform (ICTRP), Sri Lanka Clinical Trials Registry (SLCTR).

Search Terms: Covid-19 and TCM, Covid-19 and Ayurveda, Covid-19 and Sri Lankan Traditional Medicine, Clinical studies on Covid-19 from Traditional Medicine, Viral diseases and Traditional Medicine.

Analysis of Data: Obtained data were analyzed under three subheadings named; Covid-19 and TCM, Covid-19 and Ayurveda, Covid-19 and Sri Lankan Traditional Medicine. Only the clinical trials conducted by using human beings were used to gather the relevant data for this review.

Method of Data Presentation: The identified treatment procedures, preventive measures, and new formulations were presented systematically to find out evidence-based Traditional Medicinal clinical research to combat Covid-19. This review was carried out by using the published studies which report about the clinical research in TM for combat Covid-19. A comprehensive review was conducted by using the data bases; Pub Med and Science direct for studies published from 1st of December, 2019 to 1st of February, 2021.

The keywords used in this subject were Covid-19, Traditional Medicine, and clinical trials. Results were obtained only from the studies published in English while excluding commentaries and duplicate articles. The selected, appropriate articles were initially searched by reading the title and their abstracts. In this instance also, the articles which do not fulfill the requirements of inclusion criteria were excluded. After that, the remaining articles were screened by reading the complete text at the final stage.

Those articles which do not satisfactorily enrich with inclusion criteria were excluded again. Apart from that, relevant texts and Internet sources such as the International Clinical Trials Registry Platform, Sri Lanka Clinical Trials Registry were also used to gather necessary facts about this particular search. The articles which were to be included in the review was determined by an iterative consensus process at the final stage.

RESULTS: Using the above criteria, the literature search identified these articles in the databases respectively; PubMed (n=165), Science direct (n=1303). Two additional articles were searched manually by searching the reference lists in order to find the possible inclusion criteria. After removing duplicate articles, the total number of articles included in the present review is [29]. **Fig. 1** indicates the summarized search strategy.

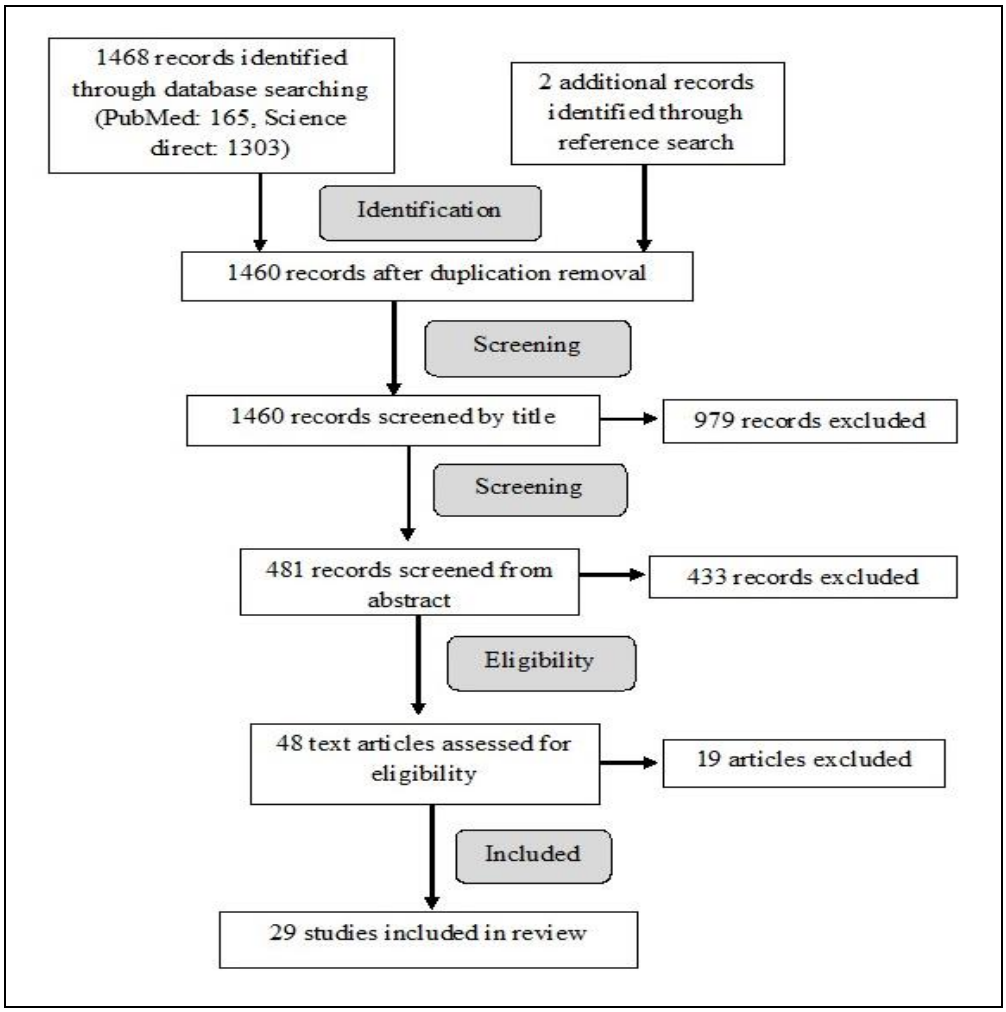

FIG. 1: SUMMARIZED SEARCH STRATEGY

TCM in the Treatment of Covid-19: A research was conducted on a novel Traditional Chinese medicine formula, Taiwan Chingguan Yihau (NRICM101) by means of clinical, pharmacological, and quality control studies [12]. The drug was given in the form of decoction which contain 10 ingredients and it has been administered to the patients with Covid-19 in Taiwan since April, 2020. There were 35 total participants for this study from two hospitals who have not undergone any improvement during their hospital stay with symptomatic treatment.

Thirteen of them shifted to NRICM101 voluntarily with the consent of their caregivers. After excluding two cases, there were 12 patients in the NRICM101 group and 21 patients in the non-NRICM101 group. It was observed that the group treated with NRICM101 got a rapid recovery compared to the non-NRICM101 group without any adverse effects. The pharmacological studies regarding this research further stated that it was due to the antiviral and anti-inflammatory effects of NRICM101.

The early intervention of TCM corresponded with a faster conversion time of pharyngeal swab and fecal nucleic acid and a shorter duration of hospital stay [13]. It was revealed by conducting research by making use of Three hundred patients admitted in a hospital of China and divided into three groups. The three groups received TCM within 7, 8–14, and more than 15 days of hospitalization, respectively. This means that group 1 received TCM treatment at the earliest stage, while group 3 received it at last. This study revealed that early intervention with TCM leads for rapid recovery by analyzing the conversion time of pharyngeal swabs, fecal nucleic acid, and patients' hospital stay. The importance of following combined treatment of TCM and Western medicine was demonstrated by conducting a twelve-day period of treatment for a critically ill patient in China who has been diagnosed with Covid-19 [14]. The patient's condition returned to the normal level during the study period, and it was monitored by taking two nasopharyngeal swabs consecutively after the treatment, which indicated the results as negative.

The evidence gathered by researching sixty-three patients showed that the efficacy of *Qingfei paidu* decoction (QPD), which is a decoction that belongs to TCM, when used in combination with Western Medicine for the treatment of COVID-19, for a period of fourteen days possess the outcomes of giving anti-inflammatory effects, as well as it could mitigate the extent of multi-organ impairment to [15]. The human exposure to TCM, *Lianhuaqingwen* (LHQW) components, and their anti-COVID-19 pharmacological activities were demonstrated by analyzing LHQW component profiles in human plasma and urine after repeatedly dosing the drug [16]. This study provided knowledge on chemical and biochemical evidence for LHQW.

The clinical efficacy of *Xuanfei Baidu* Decoction (XBD), which is herbal medicine in TCM combined with conventional drug therapy, was compared with the conventional medicine alone with forty-two patients of Covid-19 [17], where there were twenty-two patients in the XBD + conventional group and twenty patients in conventional medicine alone group. It was revealed that, after conducting the treatment procedures for a period of 1 week, the patient's clinical symptoms improved significantly when the XBD combined with conventional medicine was given. A retrospective case series conducted on fifty-five Covid-19 patients in Wuhan city of China evaluated the efficacy and safety of Chinese Medicine compared to Western Medicine [18]. The results showed that CM has more beneficial effects in the clearance of SARS-CoV-2 RNA, absorption of lung lesion opacity, and reducing the inflammation in severe COVID-19 patients. Therefore, it was stated that CM is very effective and safe for treating severe COVID-19 patients and reducing the mortality rate. The effect of *Hanshiyi* Formula (HSYF), which is a TCM, was evaluated by enrolling 721 mild and moderate COVID-19 patients, where among them, 430 HSYF users were categorized as the exposed group. In contrast, 291 were categorized as the control group. The results revealed that HSYF could significantly reduce the progression of Covid-19 into a severe stage in patients with mild to moderate levels of the disease. Furthermore, it was useful in the treatment as well as in the prevention also [19].

A randomized controlled trial (RCT) was conducted and evaluated the effects of two herbal medicines named *Jinhaoartemisia* antipyretic granules and *Huoxiangzhengqi* oral liquids in reducing common cold among the residents in China during the COVID-19 outbreak [20]. The results suggested that herbal medicine therapy could significantly reduce the risk of common cold among the residents, and it describes the usefulness of herbal medicine in the management Covid-19. A study was conducted to determine the efficacy of *Shufeng Jiedu* capsules (SFJDC), a patented herbal drug containing eight drugs used to treat viral respiratory tract infectious diseases [21].

They researched by means of analyzing the antiviral and anti-inflammatory effects of SFJDC in mouse models and then among the patients. The results indicated that the clinical recovery time of COVID-19 patients has been reduced significantly. The SFJDC therapy is much effective when used within eight days of onset of symptoms. A retrospective cohort study was conducted on 82 patients with mild and moderate Covid-19 to find out the efficacy of Tanreqing Capsule (TRQC), a herbal drug used in the TCM [22]. Twenty-five and fifty-seven cases were recruited for the treatment and control groups, respectively.

Significant reductions in the negative conversion time of fecal nucleic acid and the duration of negative conversion of pharyngeal fecal nucleic acid were observed in the treatment group compared to the control group, demonstrating the therapeutic benefits of TRQC as a herbal medicine in patients with Covid-19. The use of *Huoxiang Zhengqi* dropping pills and *Lianhua Qingwen* granules combined with western medicine for two hundred eighty-three COVID-19 patients in China were investigated [23]. And this randomized controlled clinical trial revealed that the usage of the above drugs together will promote anti-infective effects, which could be used in the management of Covid-19.

A study was conducted to investigate the association between early treatment with QingfeiPaidu decoction (QFPDD) and its clinical outcome among the Covid-19 patients in China [24]. The study was undergone with seven hundred eight two participants, and it was stated that early treatment with QFPDD could be an effective strategy to control the epidemic as it aids in favorable outcomes such as rapid patient recovery, viral shedding, less hospital stay, etc. A case study conducted and demonstrated that Professor Xu ZOU's acupuncture technique was successful in a sixty-four-year-old female patient who Covid-19 suffered. She was treated with acupuncture and Chinese herb granules for 10 days on the basis of the oral administration of moxifloxacin. The CT image of the chest indicated that the absorption of COVID-19 was significant when compared with before starting the treatment, and also the nucleic acid test of novel coronavirus was negative. This represented the value of Acupuncture therapy in the management of Covid-19 [25].

A non-randomized controlled trial was conducted among sixty patients who were diagnosed with Covid-19, and they were divided into three groups, by giving Lopinavir-Ritonavir treatment for group 1, *Huashi Baidu* Formula (a Chinese medicine formula), and Lopinavir-Ritonavir for group 2, and *Huashi Baidu* Formula for group 3 [26]. The results illustrated that the remission time of group C was the shortest, which gives evidence that, Lopinavir-Ritonavir has some efficacy in COVID-19 treatment and *Huashi Baidu* Formula might enhance this effect. A single-center, retrospective, observational study was carried out in a hospital in China from 15th January 2020 to 30th March 2020, by giving Chinese herbal medicine (CHM) granules and usual care to one group while giving only usual care to the other group [27]. The use of CHM granules could reduce the 28-day mortality rate and the time taken to reduce the fever even though there was no significant difference in clinical improvement of patients treated with CHM granules when compared with those who received usual care only. A randomized controlled trial was performed by randomizing the patients of Covid-19 to receive the usual treatment or *Lianhua qingwen* (LH) capsule, which is a Chinese herbal product, with usual treatment for a period of 14 days.

It was discovered that the recovery rate of Covid-19 patients was considerably higher in the treatment group when compared with the control group, which indicates the effectiveness of the herbal medicine[28]. The effectiveness of TCM herbal prescriptions in the combat of Covid-19 by using patients in a hospital in Wuhan, China, illustrated that death rates of those who received TCM are comparatively less than those who did not receive TCM [29]. The TCM preparations consisted of *Pericarpium Citri Reticulatae, Rhizoma Pinellia, Radix Scutellariae,* and their combinations mainly. A randomized controlled trial was conducted to evaluate the efficacy and advantages of Traditional Chinese Medicine Rehabilitation (TCMR) which was consisting of acupressure therapy and *Liu Zi Jue Qigong* for treating patients with severe COVID-19 by using 128 patients [30]. The patients were divided into two groups, and the TCMR was given to one group along with the normal guideline therapy.

The results indicated the efficacy of TCMR in the management of Covid-19. By making use of 22,065 patients of Covid-19 and randomly dividing them into 2 groups, a large scale prospective clinical study was carried out and the subjects were divided into two groups where the non-intervention group was given only the health guidance only while the intervention group was given two coordinated TCM named *Huo-xiang Zhengqi* Oral Liquid and *JinhaoJiere* Granules in addition to health guidance. The results suggested that TCM intervention could effectively treat the patients as it was safer, and there was a lower chance of

occurring adverse effects to [31]. The efficacy of TCM named *Maxingshigan-weijing* decoction was revealed by conducting an open-label 2 arm randomized controlled trial among the patients of Covid-19 in three hospitals of china [32].

The integrated treatment of Western Medicine and TCM was observed by recruiting 83 patients who were admitted in seven hospitals of China revealed that the combination of these two medical systems could give out a good curative effect on Covid-19 which was also beneficial in improving clinical symptoms, promoting the absorption of pulmonary inflammation and controlling the disease progress and hospital stay [33]. An exploratory randomized controlled trial was designed by making use of 100 cases who were in quarantine period after the close contact of Covid-19 patients and divided them into two groups a moxibustion group and a conventional intervention group [34]. In preventing diseases, TCM most abundantly uses moxibustion, which comes under acupuncture therapy, a TCM protocol used in China.

The therapeutic effect of moxibustion on Covid-19 was explored by carrying out a randomized study among 95 patients and dividing them into the moxibustion group and the basic treatment group while giving Western treatments for both groups [35]. It was revealed that moxibustion therapy could alleviate the clinical symptoms and reduce the inflammatory conditions, which concluded that, rather than using the simple routine of Western Medicine, it is better to use moxibustion therapy as a supplementary therapy along with Western Medicine. The protection provided by *Shenfu* injection, which is a TCM, against the development of organ dysfunction in critically ill patients with Covid-19 was demonstrated by designing a randomized, controlled, open-label clinical trial [36]. *Liuzijue* exercise, a traditional Chinese exercise, showed the increased function of patients discharged after following treatments for Covid-19 [37]. The study was conducted by enrolling thirty eligible patients who were discharged after treatments. The study demonstrated that 4 weeks after the intervention, maximal inspiratory pressure (MIP), peak inspiratory flow (PIF), and diaphragm movement in deep breathing (DM-DB) of patients increased significantly; meanwhile,, dyspnea was also alleviated in the subjects.

Ayurveda Medicine in the Treatment of Covid-19: A placebo-controlled randomized clinical trial was conducted to evaluate the efficacy of Ayurveda treatment regimen on asymptomatic to mildly symptomatic patients who were positive Covid-19 [38]. There were two groups named the treatment group who received Indian Traditional Ayurveda medicines, including 1 g of *Giloy Ghanvati* (*Tinospora cordifolia*), 2 g of *Swasari Ras* (traditional herbo-mineral formulation), 0.5 g each of *Ashwagandha* (*Withania somnifera*) and *Tulsi Ghanvati* (*Ocimum sanctum*). *Swasari Ras* was also administered in powdered form. 4 drops of Anu taila (A Traditional nasal drop) were also given to them. And the other group was the placebo group which received identical-looking tablets and drops. The results indicated that the Ayurveda treatment regimen could aids in faster recovery without creating any adverse effects, and it also had the ability to reduce inflammatory markers.

A randomized, open-label parallel-group study was conducted to explore the efficacy of Ayurveda medicines to combat COVID-19 [39]. This trial was carried out for 10 days by using 120 patients who were randomly divided into three groups. Among them, two groups were given Ayurveda drug intervention while the third group was the Control group. The drugs prescribed for 1st group were *Vyaghryadi Kashaya and Samshamanivati*. For the 2nd group, fine powder of *Shunthi* (*Zingiber officinale*) and paste of *Rasona* (*Allium sativum*), while the control group or the 3rd group was given Vitamin c and Paracetamol tablets. The results illustrated that groups 1 and 2 attained early recovery with viral clearance compared to Group 3. Those symptoms such as fever, sore throat, and irritation were significantly reduced in group 1 compared to groups 2 and 3. They further stated that Ayurveda drugs can act against viruses and can be used effectively against COVID-19 infection. By presenting a case report on Ayurveda intervention in a COVID-19 patient with severe hypoxia, it was revealed that a remarkable improvement occurred within a day of administration of the Ayurveda treatment regimen. Apart from that, there was a symptomatic improvement too, which showed the effectiveness of Ayurveda Medicine as an alternative for COVID-19 patients presenting with symptomatic hypoxia [40].

Apart from the above databases, the International Clinical Trials Registry Platform (ICTRP), managed by WHO, and Sri Lanka Clinical Trials Registry (SLCTR) were also searched to find out the registered TM clinical trials for Covid-19. ICTRP indicated that there was a total number of 133 trials that have been registered in the field of TCM for the combat of Covid-19, while there were 67 trials registered in the Ayurveda aspect. According to SLCTR, 2 clinical trials have been registered in Sri Lanka. In the Sri Lanka Clinical Trials Registry (SLCTR), which the Sri Lanka Medical Association manages, two clinical trials have been registered to be conducted, and still the trials are on the test. One of them is the Randomized Double-Blind Phase II Clinical Trial to Assess the Efficacy and Safety of an Ayurvedic Formulation in COVID-19 Infected Patients with the SLCTR registered number SLCTR/2021/002, which has been registered on 08.01.2021. The clinical study will be conducted at the National Institute of Infectious Diseases, Angoda, Sri Lanka. Patients who fulfill the inclusion criteria will be randomly divided into two groups. One group will receive the Link Natural Sudarshana tablet while the other group will receive the placebo [41]. Another clinical trial has been registered with the SLCTR register number SLCTR/2021/001 named, a double-blind placebo-controlled randomized parallel-group phase 1-2 proof-of-concept clinical trial on efficacy and safety of *Sri Weera Badhra Dhamma Prathishakthi Jeewa Panaya* for asymptomatic patients or patients with mild to moderate COVID-19. It will be carried out as a randomized controlled trial by participating patients of Covid-19 from Methsirisewana (affiliated to Teaching Hospital, Anuradhapura) and Nochchiyagama Divisional Hospital, which are dedicated COVID-19 treatment centers in Sri Lanka. The novel herbal preparation, which contains bees honey, pericarp, and mace of nutmeg (*Myristica fragrans*), fennel seeds in powdered form (*Foeniculum vulgare*), and juice of raw ginger rhizomes (*Zingiber officinale*) will be given to the intervention group while a placebo will be given to the other group [42]. The obtained reviews were summarized according to their research design in **Table 1.**

TABLE 1: SUMMARY OF THE RESEARCH DESIGNS

Study design	Randomize or not	Intervention drug	Con.	Outcome measured	Ref.
A clinical, pharmacological, standardization and quality control study. (A Bedside to bench study)	Not randomized	*Taiwan Chingguan Yihau* (NRICM101)	Yes	The antiviral and anti-inflammatory effects of NRICM101 indicated that it may be used to inhibit mechanisms of SARS-CoV-2 invasion and proliferation.	Keng*et al*., 2021
A retrospective cohort study	Randomized	*Tanreqing* Capsule, *Liushen* Pill, *LianhuaQingwen* Capsule and *ShufengJiedu* Capsule.	No	TCM intervention shortens hospital stay length, reduces inflammatory indicators and faster conversion time of pharyngeal swab nucleic acid and fecal nucleic acid.	Miao *et al*., 2021
A case study	Not randomized	A specific TCM formula with several herbal drugs	No	Respiratory distress and appetite quickly improved, lung lesions in CT scan largely absorbed, two consecutive nasopharyngeal swabs were negative	Kui *et al*., 2020
A clinical retrospective study	Randomized	*QingfeiPaidu* decoction (QPD)	Yes	Treatment tended to mitigate the extent of multi-organ impairment.	Siyi *et al*., 2020
A single-center, randomized, open, and multiple-dose trial	Randomized	*Lianhuaqingwen* capsule (LHQW)	Yes	LHQW components in human plasma and urine play potential roles in inhibiting SARS-CoV-2 infection.	Xiaofei*et al*., 2021
A pilot randomized controlled trial	Randomized	*Xuanfei Baidu* decoction (XBD)	Yes	Disappearance of the main symptoms is fever, fatigue, and cough. the disappearance	Wu *et al*.,2020

				of secondary symptoms, and the changes in WBC, Lymphocytes, ESR, C-reactive protein	
A retrospective case series	Randomized	*Huashi Baidu* granule, Injection of *Xiyanping, Xuebijing*, and *Shenmai*	Yes	CT imaging showed more widely lung lesion opacity absorbed, C-reactive protein level, erythrocyte sedimentation rate, serum ferritin, and myoglobin decreased, reduced inflammation	Luqi, 2021
A retrospective cohort study	Randomized	*Hanshiyi* Formula (HSYF)	Yes	The proportion of mild and moderate COVID-19 patients who progressed to severe disease status. No cases in the exposed group and 19 (6.5 %, $P < 0.001$) cases in the control group progressed to severe disease.	Jiaxing *et al*., 2020
A large prospective open-label, parallel-group, cluster randomized controlled trial	Randomized	*Jinhaoartemi-sia* antipyretic granules and *Huoxiangzhe-ngqi* oral liquids	Yes	The occurrence of patient-reported common cold symptoms, the time in days from the receipt of herbal drugs/reference manual, and the occurrence of the common cold symptoms.	Bohua*et al*.,2020
A Clinical real-world pragmatic study	Randomized	*ShufengJiedu* capsules	Yes	Patients were asymptomatic with cough and fatigue	Lu *et al*., 2020
A retrospective cohort study	Not randomized	*Tanreqing* Capsule (TRQC)	Yes	Shorter negative conversion time of fecal nucleic acid, a shorter interval of negative conversion of pharyngeal-fecal nucleic acid	Xing *et al*., 2020
A randomized controlled trial	Randomized	*HuoxiangZhengqi* dropping pills and *LianhuaQingwen* granules	Yes	Improving clinical symptoms, reducing utilization rate of anti-infective drugs, and improving patient prognosis	Mingzhong*et al*., 2020
A retrospective multicenter cohort study		*QingfeiPaidu* decoction (QFPDD)	Yes	time to recovery, days of viral shedding, duration of hospital stay and course of the disease	Nannan*et al*., 2020
A case study	Not randomized	*Xu ZOU's* acupuncture technique	No	Chest CT image indicated that the obvious absorption of COVID-19, the nucleic acid test of novel coronavirus was negative; the patient narrated no obvious discomfort.	Lan *et al*., 2020
A prospective, single-center non-randomized controlled trial	Not randomized	*Huashi Baidu* Formula	Yes	clinical remission time, clinical remission rate, time of release from quarantine, the rate of release from quarantine, clinical, biochemical indicators, safety indexes such as liver function (ALT, AST), kidney function (creatinine), and myocardial damage.	Nannan*et al*., 2020
A single-center, retrospective, observational study	Not randomized	Two CHM granules, *Chai-hu-jie-du* and *Fu-zheng-jiu-fei.*	Yes	Time taken to clinical improvement within 28 days reduced the 28-day mortality	Yuanyuan *et al*., 2020

				rate and the time to fever alleviation.	
A multicenter, prospective, randomized controlled trial	Randomized	*Lianhuaqing-wen* (LH) capsule	Yes	The median time to symptom recovery, the rate of improvement in chest computed tomography, and clinical cure.	Ke*et al*., 2020
A single-center retrospective study		TCM herbal prescription mainly consisted of *Pericarpium Citri Reticulatae, Radix Scutellariae, Rhizoma Pinellia*		Associated clinical features for the prognosis of COVID-19 and lower death rates	Zixin*et al*., 2020
A parallel-design, 2 arm, analyst assessor-blinded, randomized, controlled trial	Randomized	Acupressure therapy and *Liu Zi Jue Qigong* exercises	Yes	Measured by modified Medical Research Council Dyspnea Scale, activities of daily living barthel index scale, respiratory symptoms (rs) scale patient health questionnaire-9 (phq-9) scale.	Shuaipan*et al*., 2020
A large scale prospective clinical study	Randomized	*Huo-xiang Zhengqi* Oral Liquid and *JinhaoJiere* Granules	Yes	The difference of colds incidence between the two groups.	Bo *et al*., 2020
An open-label 2 arm randomized controlled trial	Randomized	*maxingshigan-weijing* decoction	Yes	The number of days the symptom of fever improves in the first 14 days of treatment, negative test results for SARS-CoV-2 nucleic acid, chest X-ray improvements, and rate of symptom recovery	Congcong*et al*., 2020
A prospective single-arm clinical study		*Integrated TCM and Western me-dicine*	Yes	Negative 2019-nCoV nucleic acid, hospital stay, clinical symptoms and signs scores, chest imaging	Yang*et al*., 2020
An exploratory randomized controlled trial	Randomized	Moxibustion	Yes	The symptoms changes, e.g. anxiety, emotional disturbance, fatigue, headache and diarrhea, as well as whether quarantine release and the case confirmed or not.	Mai*et al*., 2020
A randomized trial	Randomized	Moxibustion	Yes	The clinical symptom scores, WBC count, CRP, T lymphocytes value	Lin*et al*. 2020
A multicenter, randomized, controlled, open-label, two-arm ratio 1:1, parallel-group clinical trial	Randomized	*Shenfu* injection	Yes	Newly developed or exacerbated organ dysfunction, SOFA score in total, Pneumonia severity index score, Dosage of vasoactive drugs, Ventilation free days within 28 days, Length of stay in intensive care unit, 28 day mortality, The incidence of adverse drug events.	Zong*et al*., 2020
A multicenter prospective self-controlled study	Not randomized	*Liuzijue* exercise	No	The maximal inspiratory pressure (MIP), peak inspiratory flow (PIF), and diaphragm movement in deep breathing.	Yunliang*et al*., 2021
A placebo-controlled	Randomized	1 g of *Giloy Ghanvati*	Yes	Testing negative in PCR,	Ganpat *et*

randomized, double-blind pilot clinical trial.		(*Tinospora cordifolia*), 2 g of *Swasari Ras* (traditional herbo-mineral formulation), 0.5 g each of *Ashwagandha* (*Withania somnifera*) and *Tulsi Ghanvati* (*Ocimum sanctum*).		Serum levels of pro inflammatory markers like CRP, interleukin-6 and tumor necrosis factor alpha.	*al*., 2021
A randomized, open-label parallel-group study	randomized	*Swasari Ras* powder, 4 drops of Anu taila *Samshamanivati, Shunthi* and *Pipp-ali* powders, *Vyaghryadi Kashaya, Pranayama* (Bre-athing exercises)	Yes	Effect on symptoms, Effect on Real-time PCR	Adil *et al*., 2021
A case report		*Sadangapana, Guduchi, Saddharanachurna, Sukshmatriphala, Kanakasava, Indukanth*	Yes	Symptoms subsided (afebrile and vitally stable with SPO2), Negative PCR test	Jyoti *et al*., 2020

DISCUSSION: The treatment and prevention of the COVID-19 pandemic is a top priority for the world and scientists have drawn their attention towards alternative medicine such as TM, which is prepared using herbal or herb-mineral drugs materials. The available clinical studies showed that TM has the potential to combat Covid-19 substantially. It was noted that TM aids in the rapid recovery of infected patients and less hospital stay. And also, without causing any adverse effects, TM has shown the capability of treating particular conditions of patients with Covid-19. It mainly possesses the actions such as Immune modulation, anti-viral, anti-inflammatory, *etc.* The mitigation of the extension of multi-organ impairment and protection of the organs is also achieved by using the TM. It mainly consists of drugs that are favorable to human health. Therefore, organ dysfunction is also limited due to this. With the usage of TM, increased safety can be obtained for patients as well as clinical symptoms of Covid-19 could also improve by using it. Lowering the chance of relapses and promoting health and nourishment to the infected patients were also documented in the researches of followed databases. TM could reduce the mortality rate also, and therefore it is clear that not only for the treatment but also for the prevention, TM could play a major role in combatting the Covid-19 pandemic, which is the main threat to the world at present.

CONCLUSION: The TM has accumulated plenty of beneficial health effects over numerous infectious disease conditions. Up to now there is no any effective Western treatment which has been completely proven effective for Covid-19. Review data have shown the ability of supporting the therapeutic effects of TM treatment modalities. The available studies suggested that TM may be played a major role in the treatment and prevention of Covid-19 pandemic and therefore such remedies should be thoroughly investigated for further, clinical implementations in the treatment and prevention of Covid-19 pandemic.

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REFERENCES:

1. Sharma A, Tiwari S, Deb M.K and Marty JL: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. International Journal of Antimicrobial Agents 2020; 56: 106054. doi: 10.1016/j.ijantimicag 2020.106054.
2. Bulletin of the World Health Organ 2011; 89: 540-41 doi:10.2471/BLT.11.088815.
3. World Health Organization (2020) Novel coronavirus (2019-nCoV). Situation Report 11. 31 January 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4 (Accessed on 21 February 2020).
4. Tiwaria R, Dhamab K, Sharunc K, Yatood MI, Malike YS, Singhb R, Michalakf I, Sahg R, Aldanah DKB and Moralesi AJRM: COVID-19: animals, veterinary and zoonotic links. Veterinary quarterly 2020; 40: 169–182. doi.org/10.1080/01652176.2020.1766725.
5. COVID Live Update: https://www.worldometers.info (Accessed on June 26, 2021).

6. Alam MR, Md. Kabir R and Rezab S: Comorbidities might be a risk factor for the incidence of COVID-19: Evidence from a web-based survey: Preventive Medicine Reports. 2021; 21: 101319. doi: 10.1016/j.pmedr 2021; 101319.
7. Leung NHL: Transmissibility and transmission of respiratory viruses: Nature Reviews Microbiology 2021; 19: 528–545. doi.org/10.1038/s41579-021-00535-6.
8. Chen N: Epidemiological and clinical characteristics of 99 cases of 2019 novel virus pneumonia in Wuhan, china: a descriptive study 2020; 395(10223): 507-13.
9. Erin A and Todd T: How Covid-19 ravages the body. 2020. https://projects.sfchronicle.com/2020/virus-organs-graphic/.
10. Which continents have reported new variants of Covid-19. Retrieved from: https://www. aljazeera. com/news/ 2020/ 12/ 31/ which-countries-have-reported-new-variants-of-covid-19
11. Rhea VN, Hastono R, Mohammad G, Astrid FK and Nur A: (2020). Traditional herbal medicine candidates as complementary treatments for COVID-19: A review of their mechanisms, pros and cons. doi: org/10.1155/2020/2560645.
12. Keng CT, Yi CH, Chia CL, Chia IT, CTC, Chien JL, Wen CW, Sunny SL, Yu HT, Kuo, MY, Yi L. L, Jia TJ, Jian JL, Chun CL, Wen FC, Yao HK, Shen ML, Ming YL and Yi C Su: A Traditional Chinese medicine formula NRICM101 to target COVID-19 through multiple pathways: A bedside-to-bench study. Bio Medicine and Pharmacotherapy 2021; 13: 111037.
13. Miao S, Shi S, Wei Z, Xing Z, Gui X, Xuan C, Zi S, X S Lu L, Yi Z, Yi Z, Meng SQC, Yan X, Hua L, Wei, Y, Xiao C and Yun L: arly therapeutic interventions of traditional Chinese medicine in COVID-19 patients: A retrospective cohort study. J of Integrative Medi 2021; 19(3); 226-31.
14. Kui Z, Maolu T, Yang Z, Luo W, Sha L, Wei X,Xiangyan, Z and Zha Y: The combined therapy of a traditional Chinese medicine formula and western medicine for a critically ill case infected with COVID-19.Complementary therapies in Medicine 2020; 52: 102473.
15. Siyi X, Xueqi C, Bo Z, Xiaolong L.,Feng, Y, Lina S, Yan S, Xuefeng G, Renyi S, Jian W, Limi X, Xiping X, Lin J, Yanping L, Wei Z, Dongwei Z, Liang L, You Y and Rui Y: Clinical retrospective study on the efficacy of QingfeiPaidu decoction combined with Western medicine for COVID-19 treatment 2020; 129: 110500.
16. Xiaofei C, Yunlong W, Chun C, Yanqiu G, Chunyan Z, Suping W, Jiayun C, Lei Z, Lei L, Guoqing Z, Yongfang Y, Yifeng C, Mingshe Z and Caisheng W: Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 bio chromatography screening. Acta *Pharmaceutica sinica* B 2021; 11-1: 226-32.
17. Wu X, Gang W, Juan D and Wang A: Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: A pilot randomized clinical trial. Integrative Medicine Research 2020; 9-3: 100489.
18. Luqi H: Efficacy and Safety Assessment of Severe COVID-19 Patients with Chinese Medicine: a Retrospective Case Series Study at Early Stage of the COVID-19 Epidemic in Wuhan, China. Journal of Ethnopharmacology 2021; 113888.
19. Jiaxing T, Shiyan Y, Han W, Ying Z, Yujiao Z, Haoran W, Xiuyang L, Zezheng G, Yanke A, Xiaowen G, Lei Z, Liyun, H, Fengmei L, Baoyan L and Xiaolin T: Hanshiyi Formula, a medicine for Sars-CoV2 infection in China, reduced the proportion of mild and moderate Covid 19 patients turning to severe status: A cohort study. Pharmacological Study 2021; 161: 105127.
20. Bohua YZhiwei, J, Jing Y, Minghui L Jieping Z, Jianyuan T, Hong D, Jielai X, Qiaoling W, Jundong W, Hongyan X, Wenyuan L, Na Z, Haiyan L, Xiao S, Lina W, Xiaomo X and Shuguang Y: Effects and safety of herbal medicines among community dwelling residents during COVID-19 pandemic: A large prospective, randomized controlled trial (RCT). Phytomedicine 2021; 85.
21. Lu X, Yujing S, Jie SU, Thomas F,Zhenggang T, Yunfei L, Yun L, Ying L, Ronghua Z, Zihan G, Xiaolan C, Hongzhou L, Sven S and Jiedu S: promising herbal therapy for moderate COVID-19: Antiviral and anti-inflammatory properties. Pathways of Bioactive Compounds and A Clinical Real-World Pragmatic Study 2021; 85.
22. Xing Z, Yan X, Xuan C, Jia W, ZiSu Meng S, Lu L, YiZ, Yi Z, Gui X, Miao S, Xiu S, Yun L and Wei Z, Qi C: Effects of Tanreqing Capsule on the negative conversion time of nucleic acid in patients with COVID-19: A retrospective cohort study. Journal of Integrative Medicine 2020; 19: 36-41.
23. Mingzhong X, Jiaxing T, Yana Z, XiXu X M, Yi L, Miao P, Ying Z, Dengying Y, Suping L, Qing Z, An FJ, Xiuyang L, Binbin L, Manhong J, Quan L, Jinyue Z and Xiaolin TE: fficacy of Huoxiang Zhengqi dropping pills and LianhuaQingwen granules in treatment of COVID-19: A Randomized Controlled Trial 2020; 161.
24. Nannan S, Bin Honggang Y, Hongmei W, Heng G, Yuan K, Shaowen T, Yang Z, Lin T, Sihong L, Chen Z, Renbo C and WeiguoB: Association between early treatment with QingfeiPaidu decoction and favorable clinical outcomes in patients with COVID-19: A Retrospective Multicenter Cohort Study 2020; 161.
25. Lan T, Tao H and Dan: Case of Professor Xu ZOU's acupuncture technique for "benefiting kidney and strengthening anti-pathogenic qi" in promoting the absorption of COVID-19.World Journal of Acupuncture-Moxibustion 2020; 30-3: 167-70.
26. Nannan S, Lanping G, Bin L, Yongjun, B, Renbo C, Suping C, Yang C, Yingying C, Xiaodong C, Guoju D, Jing, G, Lijie H, Jianxin J, Luxing L, Bin L, Dongxu L, Hao, L, Jing L and Luqi H: Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease 2019. A non-randomized controlled trial. Phytomedicin 2020; 81.
27. Yuanyuan W, Yuntao L, Qingquan, L, Danwen, Z, Li, Z, Wenwei O, Banghan D, Xu Z, Fang Y, Bo L, Jun C, Tianzhu L, Chichen F, Qu F, Yi W, Fang L, Ailan C Cecilia S and Lundborg Z: Effect and safety of Chinese herbal medicine granules in patients with severe coronavirus disease 2019 in Wuhan, China: a retrospective, single-center study with propensity score matching. Phytomedicine 2021; 85.
28. Ke H, Weijie G, Ying B, Wei, Z, Lanjuan L, Boli Z, Qingquan L, Yuanlin S, Xingwang L, Zhongping D, Qingshan Z, Zifeng Y, Jingyi L, Mingfeng H, Lianguo R, ChaominW, Yunting Z, Zhen J and Nan Z: Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. Phytomedicine 2021; 85.
29. Zixin S, Yana Z, Kai C, Jifen L, Xiaojun M, Qing Z Jing, S, Yajuan, X, Qunsheng Z, Qiguang Z, Jinghui J, Josiah P, Baoyan L, Xuezhong Z and Xiaodong L: Clinical features and the traditional Chinese medicine therapeutic

characteristics of 293 COVID-19 inpatient cases. Frontiers of Medicine 2020; 14: 760–75. https://doi.org/10.1007/s11684-020-0803-8.
30. Baoyan L, Xuezhong Z and Xiaodong L: Clinical features and the traditional Chinese medicine therapeutic characteristics of 293 COVID-19 inpatient cases. Frontiers of Medicine 2020; 14: 760–75. https://doi.org/10.1007/s11684-020-0803-8.
31. Shuaipan Z, Qingguang Z, Chao Z, Wei C, XiaoM, Min F and Lei F: Acupressure therapy and Liu Zi Jue Qigong for pulmonary function and quality of life in patients with severe novel coronavirus pneumonia (COVID-19): A Study Protocol for A Rand Control Trial 2020; 21(1): 751.
32. Bo Y, Zhi J, JieZ, JianT, Hong D, Jie X, Shao Q, SiJ, YunL, Z W, HaiL, Xiao S Li W, Shi T Yan L Meng T, Qiao W, Jun W, Hong X, Qi, C, Sheng Y, Nian H, Jian Y, Xiao B, Qiong Z, Xiao, Chang, J, Hong L, Zheng C and ShuY: Large-scale prospective clinical study on prophylactic intervention of COVID-19 in community population using Huoxiang Zhengqi Oral liquid and Jinhao Jiere Granules 2020; 45(13): 2993-3000.
33. Congcong Z, Zhengzhong Y, Xiaoqiong P, Jizhou Z, Jiahui Z, Fan Z, Zhuocheng S, Ye Y, Ren Y and Jinguo C: Efficacy of Traditional Chinese Medicine, Maxingshigan-Weijing in the management of COVID-19 patients with severe acute respiratory syndrome: A structured summary of a study protocol for a randomized controlled trial. Trials 2020; 21: 1029. doi.org/10.1186/s13063-020-04970-3.
34. Yang X, Jiajia W, Suyun L, Lili F, Jie S, JinlingZ, Huaru Z, Kui J, Qingxia Z, Bin L and Jiansheng LA: single arm clinical study of 86 patients with common type of coronavirus disease 2019 treated by integrated traditional Chinese and Western medicine. Multicenter Case Observation from 7 Designated Hospitals in Henan Province 2020; 32(8): 922-27.
35. Mai L, Mi L, Huan Z, Jie, Y, Jian L, Kun A, Qiong L, GuoD, Wei Z, Hong Z, Xiao C and Bao L: Significance and operation mode of moxibustion intervention for the group under quarantine after close contact with COVID-19. 2020; 40(5): 457-61.
36. Lin L, Xiao X, Dong H, Wen Y, Meng Z, WeiW, Xiao D, Qiao Y, He S, Xiao S, Yong Z and Jin Yang: Effect of moxibustion on clinical symptoms, peripheral inflammatory indexes and T lymphocyte subsets in COVID-19 patients 2020; 40(12): 1271-75.
37. Zong W, Shou F Liang X, Shu L, Ke Q, Xian H, Guo Z, Liang L, Jun Z, Wen L, Bing Q, Chen Z and Peng M: Impact of Shenfu injection on a composite of organ dysfunction development in critically ill patients with coronavirus disease 2019 (COVID-19): A structured summary of a study protocol for a randomized controlled trial 2020; 21(1): 738.
38. Yunliang T, Jian J, PengS, Moyi L, Huangjun Y, Chongchong L, Liwei C, Ziwen W, Congyang Z and Zhen F: Liuzijue is a promising exercise option for rehabilitating discharged COVID-19 patient 2021; 100(6): 24564.
39. Ganpat D, Balvir S, Deepak N, Abhishek S, Deepak B, Swati H, Acharya B and Anurag V: Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. Phytomedicine 2021; 84.
40. Adil R, Devendra S, Himanshu A, Galib R, Absar A, Mahendra Y and Ahirwar P: A Randomized open label parallel group pilot study to evaluate efficacy of Ayurveda interventions in the management of Asymptomatic and Mild COVID-19 patients- Experience of Lucknow based Level hospital of Uttar Pradesh, India. Journal ofAyurveda Medicine and Integrative Medicine 2021; (In Press, Journal Pre-proof) doi:10.1016/j.jaim.2020.12.013.
41. Jyoti A and Rammanohar P: Outcomes of Ayurvedic care in a COVID-19 patient with hypoxia- A Case Report. Journal of Ayurveda and Integrative Medicine. 2020 (In Press, Corrected Proof). doi: 10.1016/j.jaim.2020.10.006.
42. Randomized Double-Blind Phase II Clinical Trial to Assess the Efficacy and Safety of an Ayurvedic Formulation, in COVID-19 Infected Patients. SLCTR /2021/ 002https://slctr.lk/trials/slctr-2021-002.
43. A double-blind placebo controlled randomized parallel-group phase 1-2 proof-of-concept clinical trial on efficacy and safety of Sri Weera Badhra Dhamma Prathishakthi Jeewa Panaya for asymptomatic patients or patients with mild to COVID-19. SLCTR/2021/001. https:// slctr.lk/trials/slctr-2021-001.

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