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Review Article

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Complementary and alternative medicine therapies and COVID-19: a systematic review

<https://doi.org/10.1515/reveh-2021-0012>

Received January 23, 2021; accepted March 23, 2021;
published online April 12, 2021

Abstract

Objectives: Despite the high prevalence of coronavirus and various treatment approaches, including complementary and alternative medicine (CAM), there is still no definitive treatment for coronavirus. The present study aimed to evaluate the effect of CAM interventions on COVID-19 patients.

Content: Four databases (Web of Science, PubMed, Scopus, and EMBASE) were searched from the inception of databases until July 16, 2020. Keywords included complementary and alternative medicine therapies and Coronavirus.

Summary and Outlook: Of the 1,137 studies searched, 14 studies performed on 972 COVID-19 patients entered the systematic review final stage. The results showed that different CAM interventions (acupuncture, Traditional Chinese medicine [TCM], relaxation, Qigong) significantly improved various psychological symptoms (depression, anxiety, stress, sleep quality, negative emotions, quality of life) and physical symptoms (inflammatory factors, physical activity, chest pain, and respiratory function) in COVID-19 patients. The results showed that various CAM

interventions have a positive effect on improving the various dimensions of coronavirus disease but since there are few studies in this regard, further studies using different CAM approaches are recommended.

Keywords: alternative medicine; complementary therapies; coronavirus; COVID-19.

Introduction

Today, the coronavirus is a global public health emergency. The disease was first reported in the city of Wuhan in December 2019 [1]. According to the latest statistics available on March 7, 2021, there are more than 117,120,303 patients with COVID-19 in the world, and more than 2,600,860 patients have died due to this disease so far [2]. The disease has affected more than 200 countries and more than 500,000 patients are added as patients every day. Coronavirus has irreversible impacts on the individual, the psychological and physical dimensions of them, as well as an undeniable economic burden on the economies of countries. According to existing statistics, coronavirus has reduced economic production in high-income, middle-income, and low-income countries by 18, 24, and 22%, respectively [3].

Coronavirus is a viral disease of unknown origin and has no specific treatment. For this reason, the most important approaches to control this disease include social distancing, contact tracing, quarantine, isolation, and the use of masks in society [3, 4]. Physical distancing, despite helping to reduce transmission of the disease, causes loneliness-related emotional problems in the long-term. Also, the sudden nature of the disease and its rapid transmission has increased stress and anxiety in all people, leading to increased mental disorders [5]. There are some approved vaccines for COVID-19 but the vaccinations is in early stages in the world [6]. Researchers worldwide are trying to find effective treatments and approaches to treat the disease and reduce its complications worldwide. These treatments include complementary and alternative

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medicine. In some countries, including India, some complementary and alternative medicine (CAM) approaches such as Ayurveda medicine have been recognized as an adjunct to other coronavirus treatments to increase immunity and reduce the subsequent stress [7]. To the best knowledge of the researchers, since it is a novel disease, no comprehensive study has been conducted on the effects of CAM interventions on the coronavirus. Therefore, the present study aimed to investigate the effect of CAM interventions on COVID-19 patients.

Materials and methods

Design and eligibility criteria

The present systematic study was performed using the Cochrane handbook and was reported with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [8]. The protocol did not register. All case report, case series, quasi-experimental, and Clinical trial studies that examined the effects of CAM interventions on COVID-19 patients were included. No limits were applied for language and time of studies included. Reviews and qualitative studies were excluded. CAM interventions in five specialized areas included: natural products, mind-body therapies, alternative medical systems, manipulative and body-based methods, and energy therapies.

Search strategy

In this study, international databases (Web of Science, PubMed, Scopus, and EMBASE), and Preprint Databases (preprints.org, biorxiv.org) were searched from the inception of databases until January 16, 2021. Also, PROSPERO databases were searched to achieve more results. Two researchers searched the articles separately. MESH, Emtree, and related free words were used to prepare the keywords. Keywords included complementary and alternative medicine therapies and Coronavirus (Supplementary Table 1).

Study selection

After searching the databases, the articles were entered into EndNote software. Then Duplicate articles were removed using a valid method [9]. In continue, the titles of the articles were examined in terms of relevance, and the irrelevant ones were removed in the screening phase. The remaining articles were reviewed for inclusion criteria and

related items were entered. The reason for the exclusion of an article was written. Then the methodological quality of the studies was examined and the extraction stage was begun. Two researchers (SB, MB) carried out the screening stage and selection of studies separately. In cases where there was a disagreement between two researchers, the third person was asked to help solve the problem. The items extracted included: main cam category, subcategory, author (year), country, study characteristics (number of patients), age (mean or range), gender (male/female), study design, outcome measurement (outcome, instrument, quality of study), intervention details, result.

Quality assessment

To evaluate the quality of randomized controlled trial (RCT) and quasi-experimental studies JADAD scale [10] and JBI tool [11] were used, respectively. In the JADAD tool, three key methodological components, including randomization, blinding, and withdrawals or dropouts were evaluated. In the JADAD tool, studies were assigned scores 1–5, with higher scores indicating higher methodological quality (Supplementary Table 2). The JBI quasi-experimental appraisal tool was used to evaluate quasi-experimental studies (Supplementary Table 3).

Results

Study selection

Of the 1,137 articles provided by search in four databases, only 840 non-duplicate articles were entered in the next stage. Titles and abstracts of 840 articles reviewed according to inclusion criteria and relevance to the purpose of the study and 804 articles were excluded accordingly. Out of the remaining 36 articles, 14 articles entered the final stage of the systematic review phase. Of the 22 excluded studies eight were Narrative Review, one was qualitative and 13 were Review protocols (Figure 1).

Study characteristics

Fourteen studies (four RCTs, two retrospective cohorts, three Quasi-experimental, three case reports, and one case series) conducted on 972 patients with COVID-19 entered the final stage [12–25]. Most of studies conducted in China in 2020 (n=13). The number of participants in various studies was between 1 and 300. The mean age of participants was also

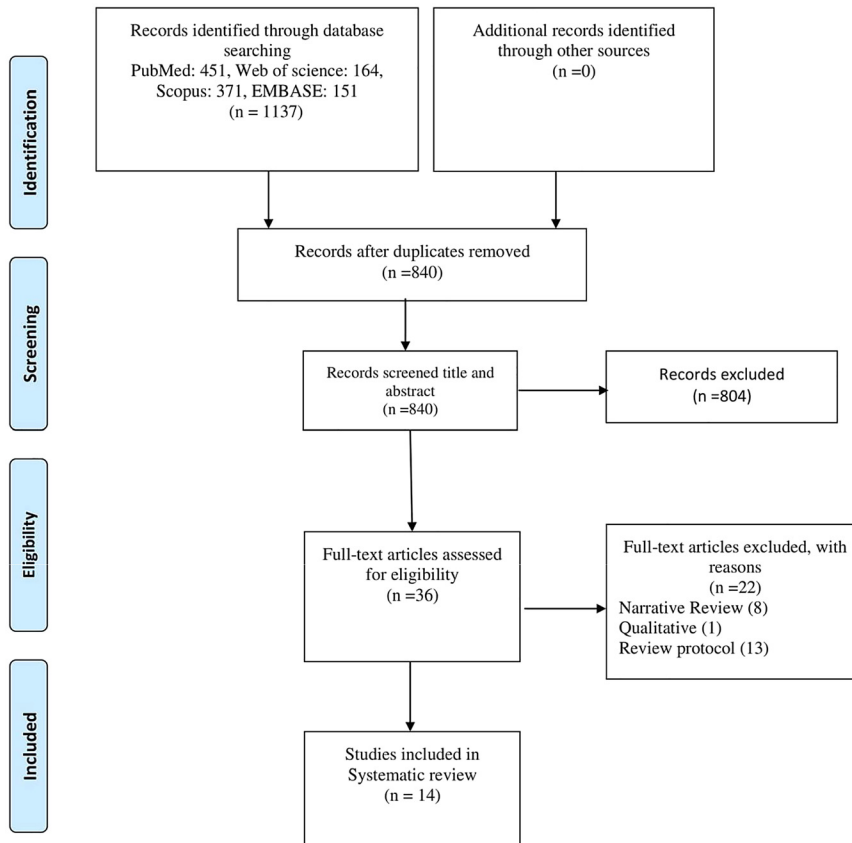


Figure 1: Study selection process.

between 30 and 81 years. Based on the categories of CAM therapies, seven studies were performed based on the main category of alternative medical systems using acupuncture and Traditional Chinese medicine (TCM). Five studies were performed in the main category of mind–body therapies using the relaxation approach. Also, two studies were performed in the main category of energy therapies using Qigong method. In the included studies, the effect of different CAM interventions on different psychological (depression, anxiety, stress, sleep quality, negative emotions, quality of life) and physical dimensions (inflammatory factors, physical activity, chest pain, and appetite level) were investigated. Standard questioners such as Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) were used to measure on psychological and physical outcomes (Table 1).

Effect of complementary and alternative medicine interventions on COVID-19 patients

Alternative medical systems: acupuncture, TCM

Seven studies used alternative medical systems approaches conducted on 711 COVID-19 patients entered

the final stage. Three studies were performed using the approach acupuncture and four studies were based on the approach. Seven studies were performed on 711. The results showed that studies that used acupuncture improved negative symptoms, regain the consciousness, chest distress, and appetite [13, 15, 22]. The results also showed that TCM improves the conversion time of fecal nucleic acid, length of hospital stay, and inflammatory markers and COVID-19 symptoms [18, 21, 23, 24].

Mind-body therapies

Relaxation

Five studies include three clinical trials, one clinical observational study and one case report performed on 212 patients with a mean age of 30–68 years, were included in the present study [14, 16, 17, 19, 20]. In the included studies, COVID-19 patients received various relaxation interventions (breathing relaxation training, mindfulness, Jacobson's Relaxation Technique, and respiratory muscle training) for 10–50 min for 5 days to 6 weeks. Regarding relaxation, the results of the study showed that relaxation improves the psychological dimensions (depression, anxiety; stress, sleep quality and quality of life) and the

Table 1: Description of the study characteristics, outcome, measurement, interventions and results.

CAM main category	Study, country	Study and participates characteristics CAM category/subcategory/type of study/participants/age/gender/ outcome and method of measurement	Intervention and control group	Results
Alternative medical systems	Huang, XB (2020), China [15]	Acupuncture/quasi-experimental/42/49.5/NR/negative emotions, chest distress, and appetite	Participants received heat-sensitive moxibustion at the acupoint area of Shenque (CV 8) and Tianshu (ST 25). Heat-sensitive moxibustion for 20, 40 min, and 1 h/no control group.	Reduce the negative emotions. Improve the symptoms of chest distress and impaired appetite.
	Gong, Y (2020), China [13]	Acupuncture/case series/2/81.72/female: 2/improve symptoms	The combined treatment of acupuncture with the oral administration of “Shanghai leishen No. 1 formula” was given every day. The prescription was modified weekly according the symptoms of the patients.	Improve the chest oppression, shortness of breath and dull pain in epigastric region were presented on exertion.
	Yeh, B (2021), Taiwan [22]	Acupuncture/case report/1/73/male: 1/regain the consciousness	Acupuncture treatment three times a week was conducted. The needles were retained for 30 min.	Improve the GCS score and regain the consciousness.
	Shi, M-y (2021), China [18]	Traditional Chinese medicine/retrospective cohort/300/81.72/female: 2/conversion time of fecal nucleic acid, length of hospital stay, and inflammatory markers (leukocyte count, and lymphocyte count and percentage)	Chinese patent medicines used included Tanreqing capsule, Liushen pill, Lianhua Qingwen capsule (granule) and Shufeng Jiedu capsule.	Improve the conversion time of pharyngeal swab and fecal nucleic acid, as well as shorter length of hospital stay, and significant effect on level of lymphocyte percentage and leukocyte count.
	Xiao, M (2020), China [21]	Traditional Chinese medicine/RCT/283/54/female: 128, male: 155/improve symptoms	Patients receive Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules and Linahua granules, both combined with western medicine, in 14 days.	Improve the anorexia, limb pain, fatigue, chest tightness, and shortness of breath.
	Zhang, K (2020), China [23]	Traditional Chinese medicine/case report/1/58/female/improve symptoms	Patients receive traditional Chinese medicine.	Improve the respiratory distress and appetite.
	Zhang, X (2020), China [24]	Traditional Chinese medicine/retrospective cohort study/82/58/female/duration of negative conversion of pharyngeal-fecal nucleic acid, and the improvement in the level of immune indicators such as T-cell subsets (CD3, CD4 and CD45) were monitored	The treatment group was given TRQC orally three times a day, three pills each time.	Shorter negative conversion time of fecal nucleic acid. The level of CD3 ⁺ T cells increased. No significant effect on CD4 ⁺ T cells and CD45 ⁺ T.
Mind-body therapies	Wei, N (2020), China [19]	Relaxation/RCT/26/40.8/Male: 16, female: 10/depression (using PHQ-9) and anxiety (using GAD-7)	Internet-based integrated intervention (intervention group): self-help intervention containing four main components: breathing relaxation training, mindfulness (body scan), “refuge” skills, and butterfly hug method. 50 min, every day for two weeks/routine care in control group.	Decrease the depression and anxiety.
	Liu, K (2020), China [16]	Relaxation/RCT/51/59/Male: 28, female: 23/anxiety (using STAI) and sleep quality (using SRSS)	Relaxation using Jacobson’s relaxation techniques (progressive muscle relaxation and deep breathing) 20–30 min each day, training for five consecutive days/no control group.	Reduce anxiety and improve sleep quality.
	Huang, J (2020), China [14]	Relaxation/case report/1/30/female: 1/anxiety (using HAMA) and depression (using HAMD)	Techniques included mindfulness and relaxation exercise, distress	Improve the anxiety and depression.

Table 1: (continued)

CAM main category	Study, country	Study and participates characteristics CAM category/subcategory/type of study/participants/age/gender/outcome and method of measurement	Intervention and control group	Results
			tolerance skills, and interpersonal relationship skills.	
	Liu, K (2020), China [16]	Relaxation/RCT/72/68/female: 23, male: 49/respiratory function (checked using spirometer), QoL (using SF-36) and psychological function (depression and anxiety using SDS and SAS)	Patients received six weeks of respiratory rehabilitation (1. respiratory muscle training; 2. cough exercise; 3. diaphragmatic training; 4. stretching exercise; and 5. home exercise) two sessions per week, once a day for 10 min.	Improve the respiratory symptoms, quality of life and anxiety. No effect on depression.
	Xiao, C (2020), China [20]	Relaxation/clinical observational study/79/58–59/female: 35, male: 44/depression (using PHQ-9) and anxiety (using GAD-7) and sleep quality (using PSQI)	The observation group received progressive muscle relaxation training, in addition to the routine treatment and nursing bed 30 min before getting up early and 30 min before going to bed/the control group received routine treatment and nursing.	Improve the depression and anxiety and sleep quality.
Energy therapies	Chen, JM (2020), China [12]	Qigong/quasi-experimental/10/50.2/male: 6, female: 4/physical activity, perceptions of dyspnea, and quality of life. Measures NR	Thirty minutes exercise every day for six weeks (two weeks in the hospital, four weeks after discharge from hospital)/NR.	Improve the physical activity, perceptions of dyspnea, and quality of life.
	Zhao, J (2020), China [25]	Qi gong/quasi-experimental/39/50/male: 22, female: 17/inflammation factors detected using radioimmunoassay method for detecting the content of IL-6, IL-8, IL-2R, TNF- α , PCT. And lymphocyte subsets (the levels of CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , and the ratios of CD4 ⁺ /CD8 ⁺) detected using flow cytometry	Two weeks two groups received normal interventions including bed rest and supportive treatments; ensuring sufficient calories and water intake; maintaining water-electrolyte balance and homeostasis, and strengthening psychotherapy for older children when necessary. The ICW group received the fifth edition recommendation's CM prescription extra orally for two weeks/NR.	Improve the level of IL-6 and TNF- α . No effect on WBC#, N#, L#, hs-CRP, CD4, and CD8.

physical dimension (respiratory function) of COVID-19 patients.

including IL-6 and tumor necrosis factor (TNF)- α , it does not affect WBC, hs-CRP, and CD4 [25].

Energy therapies

Qigong

Two quasi-experimental studies performed on 49 individuals (M: 28, F: 21) with a mean age of 50 years, were included in the present study [12, 25]. Chen, J. M. investigated the effect of Qigong on physical activity, dyspnea, and quality of life [12]. The intervention was that patients performed the exercise for 30 min a day for six weeks. Qigong improved physical activity, reduced dyspnea, and improved patients' quality of life. Zhao, J.'s study also showed that although Qigong improved some inflammatory factors,

Discussion

COVID-19 is the most important public health emergency worldwide. This systematic review study was performed to evaluate the effect of CAM therapies on COVID-19 patients. Fourteen studies performed on 972 COVID-19 patients, were included in the present study. The results of the present study showed that different CAM interventions (acupuncture, relaxation, and Qigong) significantly improved the different psychological and physical dimensions of COVID-19 patients.

Acupuncture studies have shown that it reduces negative emotions, chest pain, and improves appetite levels, which is consistent with previous studies suggesting a reduction in negative emotions and anxiety among addicts' population [26], health care workers [27]. The results of the present study also showed an improvement in chest pain, which is consistent with a previous study which showed that acupuncture could be used as an actual treatment to reduce chest pain [28]. However, in contrast to the present study, the previous study on obese individuals showed that acupuncture reduces appetite, which can be due to different study populations and different sample sizes, and duration of the intervention in the two studies [29].

Also the results show TCM can improve the conversion time of fecal nucleic acid, length of hospital stay, and inflammatory markers which consistent with previous studies [30–32].

Regarding relaxation, studies have shown that this technique has a significant effect on improving the psychological and physical dimensions of COVID-19 patients. These dimensions include stress, anxiety, depression, and sleep quality and quality of life. Concerning stress, the results of the present study are consistent with studies conducted in different communities, including patients with breast cancer [33], students [34], and quality of life of outpatients [35]. In contrast to the present study, the C Calder Calisi's study showed that relaxation did not have a significant effect on reducing stress among nurses, which could be due to differences in methodology and type of stress experienced among the participants of the two studies and the intensity of stress experienced [36]. The study also show relaxation and respiratory rehabilitation improve the Respiratory function of COVID-19 patients that consistent with previous studies conducted among stroke patients [37], and lung cancer [38].

Regarding anxiety, the results of the present study were consistent with studies conducted on women with breast cancer [33], the elderly [39] and inconsistent with Toosi et al.'s study performed on mothers and relaxation. Toosi et al. showed that relaxation did not affect reducing anxiety levels, which could be due to the differences in the type and severity of perceived anxiety, the difference in the type of community studied, and the type of relaxation technique used in the two studies [40]. The results of Huang, J study showed that relaxation improves anxiety and depression, which is in line with previous studies [41, 42].

About depression, the results of the present study were consistent with previous studies on cancer patients [33], the general population of the elderly [39], and the general population of adults [43]. About Qigong, the results

showed that Qigong improved physical activity, increased quality of life, and regulated inflammatory markers. Regarding the improvement of physical activities, the results of the present study were consistent with the study performed on chronic obstructive pulmonary disease (COPD) patients [44]. Regarding the quality of life, the results were consistent with the study conducted on patients with Parkinson's disease [45].

About Qigong studies showed it improved physical activity, reduced dyspnea, and improved patients' quality of life which in line with previous studies conducted on patients with infections [46], and quality of life of cancer patients [47].

Overall, the effectiveness of studies on COVID-19 patients seems to be consistent with previous studies conducted in different communities. Considering the increasing prevalence of COVID-19 and the lack of definitive medication, equipment shortages, manpower shortages, and burnout, especially in less developed countries, it seems that different CAM approaches, which have no side effects for patients, especially for those with mild cases, which make up the largest number of patients, can be used as a preventive approach, especially in the face of COVID-19, as a global stressful situation with the help of specialists. Since physical distancing and social distancing are the main preventions for the spread of COVID-19, many CAM treatment approaches such as massage, relaxation, Qigong, meditation, music therapy, yoga, dance therapy, and energy therapy can be used, training patients and volunteers through online platforms.

Limitations

The present study included limitations that should be considered when interpreting the results.

- (1) Since a short time has passed since the disease onset, a small number of studies entered the final stage; therefore, this review study should be repeated after conducting studies based on different CAM approaches on COVID-19 patients.
- (2) It was not possible to perform the meta-analysis because various approaches were used in the included studies, as well as the different durations and the severity rates of the disease.
- (3) In all the included studies, the side effects of the approaches were not stated; therefore, this point should be taken into account when using the results.
- (4) The sample size of the studies entered was small and they were conducted in a short period, which limits the generalization of the study results.

Strengths

To the best of the researchers' knowledge, this is the first study that investigates the effects of CAM interventions exclusively on COVID-19 patients. Also, a systematic scientific review approach based on international guidelines (Cochrane, PRISMA) was used to conduct the study.

Conclusion

The results of the present study revealed that different CAM interventions (acupuncture, relaxation, and Qigong) improved various psychological (depression, anxiety, stress, sleep quality, negative emotions, quality of life) and physical symptoms (inflammatory factors, physical activity, chest pain, and appetite level) in COVID-19 patients. The results also showed that various interventions could be used to improve other symptoms of COVID-19 by observing safety recommendations. Considering the number of studies entered, the number of participants, limited interventions, it is suggested to carry out further studies with a larger sample size using different approaches to CAM.

Research funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions: All authors contributed equally. All authors were responsible for all aspects of the work throughout the entire process.

Competing interests: The authors declare that they have no conflicts of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

Data availability: All data used to support the findings of this study can be made available from the corresponding author upon request.

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Supplementary Material: The online version of this article offers supplementary material (<https://doi.org/10.1515/reveh-2021-0012>).