Complementary and Alternative Medicine approach to mitigate symptoms of Post-Acute Sequelae of SARS-CoV-2 infection and similar diseases.

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Introduction

As of early 2022, according to the Centers for Disease Control, the COVID-19 pandemic has killed over one million Americans. The World Health Organization states that almost seven million have died worldwide and there have been 540 million cases to date. One unfortunate result for many who survived COVID-19 is an insidious condition called Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), formerly Post-Acute COVID-19 Syndrome, in which there are no known treatments. Chen et. al, 2022 purports about 40% of those who contract COVID-19 will have some PASC symptom. While the Centers for Disease Control states about 20% of Americans 18 and older and 25% of those 65 and older (Bull-Otterson et. al, 2022) will have some PASC symptom. The American Academy of Physical Medicine and Rehabilitation estimates there are 26 million PASC cases just in the United States (AAPM&R, 2022). PASC affects all ages and sexes. It appears to affect women over 20% more than men (PHOSP-COVID Collaborative Group, 2022 and Sylvester et. al, 2022). There are between 50-62 types of PASC symptoms that can last more than one year, and for some, develop into life-long issues, similar to autoimmune disorders such chronic fatigue syndrome (CFS) (Lopez et. al, 2021; Subramanian et. al, 2022). The World Health Organization states ominously that PASC cases seem to be growing, not abating.

Previous studies have shown that with similar autoimmune disorders to PASC, such as fibromyalgia and CFS, the dysfunctional impact on one's daily routine is palpable. Aside from physical maladies, mental fatigue and other psychological disorders are common. It seems that research during the little time that PASC has been deemed a disease is that it is more severe than fibromyalgia or CFS. If so many who contract COVID-19 continue to get PASC, that could mean

one person in every two families in the United States could be afflicted. Aside from the mental and physical toll for those with PASC, the burden family and friends must carry to care for PASC sufferers will be significant. Moreover, the strain on the treatment and rehabilitation healthcare sectors may be overwhelmed with treating PASC. Until more clarity is brought to how best to treat and manage PASC, there will be an inordinate number of those who will not be able to function, which will affect their ability to take care of themselves, their families, hold down jobs, among others. Tabacof et. al (2022) state that some respondents report that they have not worked at full capacity one year after they got COVID-19. The economic toll of these confluence of factors are too new to ascertain.

The official diagnosis for PASC are symptoms that last for 12 weeks or more. The experience of these "long-haul" COVID-19 patients is similar to other post-viral metabolic dysfunction disorders such as myalgic encephalomyelitis, also known as chronic fatigue syndrome (CFS), chronic post-SARS syndrome, the results of the SARS epidemic in the early aughts, fibromyalgia, Gulf War syndrome, and postural orthostatic tachycardia syndrome (POTS). Like other viruses that lead to the aforementioned conditions, coronavirus SARS-CoV-2, which causes the disease COVID-19, appears to induce B immune cell hyper-activation, which become weapons called autoantibodies that attack one's own tissue (Yazdanpanah & Rezaei, 2022). PASC is often a result of these autoantibodies that do not "turn off". Moreover, another problem often seen in PASC patients are overactive mast cells similar to what is seen in mast cell activation syndrome (Weinstock et. al, 2021). COVID-19 has been found to spread to almost every organ system. For example, in the first study to use magnetic resonance brain imaging (MRI) before and after COVID-19, Douaud, Lee, & Alfaro-Almagro

(2022) saw decreased gray matter, an overall reduction in brain volume, and cognitive decline. Not surprisingly, the drop in brain volume near the olfactory (smell) part of the brain, as anosmia, or loss of smell, is common to PASC patients (Zazhytska et. al, 2022). Neurocognitive and psychiatric symptoms of mental illness, including posttraumatic stress disorder (PTSD), are alarmingly high among patients who had COVID-19, even among those who were not hospitalized with the virus, (Anxiety and Depression Association of America Conference 2022). In addition, COVID-19 causes dramatic changes and impairment of mitochondrial function (Alfarouk et. al, 2021). Energy production in the cells and innate immunity are then impaired, which explains extreme fatigue many experience. Those who recover from a mild case of COVID-19 appear to have a 40% elevated risk for new-onset type 2 diabetes (Rathmann, Kuss & Kostev, 2022). The "brain fog" reported by some after COVID-19 shows striking similarities to the condition known as "chemo brain" - the mental cloudiness some people experience during and after cancer treatment, according to Shen et. al (2022).

It seems that much is now known about the deleterious effects of PASC. However, there is no consensus on which treatment(s) are best for PASC, especially as it pertains to which complementary and alternative therapies (CAM) may be successful in mitigating symptoms of PASC. The existing literature seems to indicate that CAM, directed towards oral and gut dysbiosis (Liu et. al, 2022 and Alharbi et. al, 2022), breathing therapy (Philip et. al, 2022), diet and nutrients (Motti et. al, 2022 and Barrea et. al, 2022), aromatherapy, and medicinal plants (Mukherjee et. al, 2022 and Bardelčíková et. al, 2022), may be beneficial for PASC sufferers. With regard to similar autoimmune disorders such as CFS, CAM seems best suited to assist by mitigating gut dysbiosis and through nutrient supplementation (Roth, Chan & Jonas, 2021 and

Bjørklund et. al, 2019). The goal of this literature review is to examine the CAM approach to mitigate symptoms of PASC and similar diseases to PASC, such as CFS. From this review, the hope is that the results will elucidate which CAM therapies may be used beneficially to support not only PASC, but similar, deleterious autoimmune disorders such as CFS.

Methods

The database PubMed was searched for relevant studies on Post-Acute Sequelae of SARS-CoV-2 Infections (PASC) and similar autoimmune disorders from 2017 through 2022, without geographical limitations. Post-COVID research is only available from the last two years, whereas similar autoimmune disorders to post-COVID is relevant going back at least 5 years.

The following search string was used and modified in the database to investigate the existing research for how complementary and alternative medicine (CAM) supports PASC. To narrow the search for review studies, "free full text," "review," "systematic review," and “publication within the last 5 years” were chosen to assess if there was enough research to support my topic. To narrow the search for primary studies, “free full text,” “clinical trial,” “randomized clinical trial,” and “publication within the last 5 years” were chosen. Search keywords "post-COVID syndrome," "long COVID," and "post-Acute COVID-19 syndrome" were used to support the introduction because there was very little on PASC because it is such a new term. For the results section, keywords such as "post COVID acupuncture," "post COVID Ayurvedic," and other CAM therapy keywords were used. For similar autoimmune disorders to PASC that had been shown improvement with CAM, both review categories and clinical trials were included in the search. Search keywords such as "fibromyalgia acupuncture" or "fibromyalgia Ayurvedic," were used and then modified using chronic fatigue syndrome.

Studies were included if they were peer-reviewed, except for one relevant preprint study, and were all from scientific journals. Studies were excluded if they were not peer-reviewed, were from books and articles, and were not in English or at least translatable.

Results

Post-acute sequelae of SARS-CoV-2 infection (PASC) cases are not abating, only increasing, according to the World Health Organization. According to the Centers for Disease Control, PASC refers to new, returning, or ongoing health problems experienced by people four or more weeks after initial coronavirus infection. Symptoms are vast, but fatigue, brain fog, and shortness of breath are three of the most frequent complaints. Without any known treatments for PASC, it was important to examine similar conditions to assess if, or what, CAM therapies were used successfully in the past. There were a few beneficial studies elucidated below, but overall, it seemed there was a paucity of data supporting CAM therapies for similar conditions to PASC.

An example of a condition that is similar to PASC is CFS. CAM therapies have been used for CFS, although the data is scant. In a review study from Bjørklund et. al (2019), the authors postulated that CFS cases may be the result of viral infections that triggered autoimmunity due to unresolved inflammation. Instead of CFS, some experts even call it postviral fatigue syndrome. The authors admitted that there is still much unknown about CFS because it still has not been thoroughly studied. They suggest CFS symptoms can come and go, especially if it was caused by a virus such as herpes, which never leaves the body. In times of great stress and immune susceptibility, CFS patients can experience deleterious symptoms from herpes outbreaks, while at other times, there are no symptoms at all. The authors suggested multiple nutrient deficiencies may be linked to CFS. For example, low selenium intake or deficiency, as well as a skewed ratio

of omega-6 to omega-3 fatty acids, can lead to overexpression of the immune system if not addressed. Moreover, the authors reminded us that pathogens can adversely affect gut dysbiosis, and without rebalancing good and bad gut bacteria, long-term dysbiosis from a viral offender can affect multiple organ systems. Another biochemical process that can lead to CFS is oxidative damage, due to the inability to quench the tsunami of free radicals produced during viral illness. They suggested CFS sufferers may benefit from optimal intake of antioxidants through CAM therapies such as diet optimization, oxygen therapy, targeted nutraceuticals, and mitochondrial resuscitation. What seemed to be one of the most important parallels between PASC and conditions like CFS was mitochondrial damage from depletion and inadequate detoxification (autophagy). Viral illness can destroy mitochondria, which in turn reduces cellular energy, leading to fatigue, which is a common symptom in CFSD and PASC sufferers. The authors highlighted several studies for mitochondrial resuscitation through nutritional intervention, one of which will be analyzed in the next paragraph. Because of the multitude of symptoms that encompass CFS, the authors admitted that it is very difficult to offer a specific CAM recommendation. In addition, CAM therapies such as nutrition have only been presented recently, and while several studies were compelling, they were not copious in number, small in number of participants, and few of randomized trial design, according to Bjørklund et. al (2019).

Furthermore, one such study that explained CAM benefits for CFS through mitochondrial resuscitation, Castro-Marrero et. al (2021) performed a first-of-its-kind, prospective, randomized, double-blind, placebo-controlled trial to assess the efficacy of nutraceuticals Coenzyme Q10 and NADH (reduced form of nicotinamide adenine dinucleotide) for improving symptoms in CFS patients. This type of trial is considered the gold standard in allopathy. The authors purported

that the two nutraceuticals could improve symptoms through reduction of oxidative distress and mitochondrial resuscitation. The 8-week trial consisted of 104 CFS patients receiving 200 mg. Coenzyme Q10 and 20 mg. NADH (reduced form of nicotinamide adenine dinucleotide) or 103 patients receiving placebo once daily. 19 subjects in the control group dropped out due to minor adverse effects, as did 11 in the placebo group. Another 16 subjects withdrew for difficulty adhering to the study structure. Of the 144 subjects left, there were significant improvements in fatigue, sleep quality, and overall physical functioning when screened after 4 and 8 weeks. Limitations began with the subjects, who were all caucasian women. Control supplement and placebo were donated by a supplement company who gave financial support and an honorarium to the lead author of the study. Even so, there is potential for a parallel to be made between this CAM treatment for CFS-related perceived cognitive fatigue and PASC-related perceived cognitive fatigue. The researchers could structure a new study in similar fashion, using PASC subjects instead. In conclusion, while these two aforementioned studies were encouraging, the data supporting CAM therapies to benefit CFS were thin. Thus, as for their effectiveness for PASC, it has yet to be determined.

Meanwhile, existing literature was examined to assess if CAM therapies mitigated PASC symptoms. Data on CAM therapies to benefit PASC sufferers seemed much more abundant than for similar conditions such as CSF. One such review study showed similar improvement with PASC to CFS using nutrients. A group of authors led by Motti et. al (2022) performed a review of all literature for nutrients for all phases of COVID-19, including PASC, through January 2022. The authors elucidated numerous nutrients that protect against neuroinflammation and oxidative stress, including B-vitamins, vitamins C, D, and E, omega-3 fish oil, and minerals such as

selenium and zinc. The authors specifically referred to brain fog, a common symptom of PASC, which could be the result of over-exacerbation of unresolved mast cell activity. The flavonoids quercetin and luteolin were specifically highlighted for their ability to ameliorate overactive mast cell activity. The authors mentioned several times in the review that because of fast-changing SARS-CoV-2 variants, the focus should not be on eradication, but prevention of severe symptoms and treating long-term symptoms in recovering individuals. Thus, the authors believe CAM, especially in the form of nutrients, are poised to assist. Even with 159 references, it is difficult for the authors to make any definitive conclusions because many of the studies were small and stated that larger, controlled trials needed to be initiated. For the purposes of PASC, there were only 35 references reviewed. The authors referred to the fact that because daily value (DV) of vitamins and minerals needed revision, they suspect that most human beings are currently in need of one or more micronutrients that puts them at a disadvantage to prevent, fight, and recover from a virus such as SARS-CoV-2.

In addition to nutrients, a review by Mukherjee et. al (2022) went back 18 years to the little known 2002-2003 SARS-CoV-2 outbreak to assess how herbs used back then could help prevent complications from the current SARS-CoV-2 outbreak. The authors also canvassed available herbal data for the current outbreak. 46 trials for plant-based phytochemicals and 64 trials for traditional Chinese medicine (TCM) were found, some of which are still incomplete. Other traditional medicines found in Africa and India were also cited. The authors described numerous herbs used successfully to support SARS-CoV-2-induced PASC symptoms such as cardiac, kidney, liver and lung complications, mental problems, and Parkinsonism. More common herbs known in the West such as andrographis, ashwagandha, cinnamon, and curcumin

were cited in numerous places for their benefits, among myriad other plant-based agents used around the world. The authors purported that even though many of the herbs have been used as traditional medicines in numerous cultures, most data were structured via animal, in-vitro, in-vivo, in-silico, or anecdotal clinical. They stated there is much unknown about the mechanisms of the herbs and large, human clinical trials are necessary. However, the authors suggested that in several countries like India and China, who use a combination of traditional and conventional medicine, the rest of the world should take notice of their results in dealing with the pandemic so far. Funding came from the Indian government, which is invested in Ayurveda, but it is difficult to discern if this should be considered a conflict of interest.

Nutrients and herbs are two CAM therapies that may support PASC. However, when multiple CAM therapies are used together, the benefits to patients may be even more significant. A case study by Roth, Chan, and Jonas (2021) encapsulated how multimodal use of CAM may benefit those with PASC. Aside from laying out the impact and etiology of PASC, the authors suggested CAM therapies for low income minority areas. For example, blacks often use CAM to replace the lack of accessible conventional healthcare treatments. The authors cited case studies in a culturally diverse clinic, Jamaica Hospital Medical Center in Queens. The clinic took a unique approach serving PASC sufferers utilizing conventional and CAM therapies including anti-inflammatory diets, mindfulness, yoga, journaling, meditation, guided imagery, breathing exercises, and physical exercise. The authors went into detail of two specific cases to show how the therapies were utilized and proved successful after only a period of three months. The study only focused on CAM success at one 404-bed clinic and two case study examples, but when

looking for studies that embody the essence of CAM, the authors were vociferous in their assessment that a combination of therapies for PASC should be the norm.

When reviewing single study literature to assess CAM's benefits for PASC, there were numerous categories that dominated. The first category was nutrients, nutrient deficiency, and nutrient supplementation. In many countries, there was an emphasis placed on the importance of vitamin D levels during the pandemic. Research emphasis was also directed to those with PASC. Hussein et. al (2022) used a cross-sectional study to evaluate vitamin D deficiency in 219 patients from one post-COVID clinic to understand if deficiency could be related to PASC. The authors state that 84% of PASC subjects were vitamin D deficient, 11.4% were insufficient, and 4.9% had normal levels. In those with normal levels, 90% had been taking a multivitamin. The authors noted that lower vitamin D levels were associated with abnormal inflammatory indices, such as high C-reactive protein, low ferritin, and high creatinine. The clinic was in Egypt, which receives copious amounts of sun throughout the year. Thus, the authors stated that if these large percentages of deficiency exist in Egypt, they are more likely far worse in countries that do not get as much sun. However, the authors purported that given the size and structure of the study, there was not enough to show causation.

While the study done by Mohamed Hussein et. al (2022) exhibited significant vitamin D deficiency in their post-COVID clinic patients, Townsend et. al (2021) found different results. An experimental study of 149 patients at a PASC clinic in Ireland were tested for vitamin D deficiency. 66% had sufficient vitamin D levels, 24% were insufficient, and 9% were deficient. The author pointed out that 10% of the subjects were taking vitamin D supplements and a larger number of non-caucasians were vitamin D deficient. When assessing fatigue scores in all

subjects, there was no difference between vitamin D status and better fatigue scores. Most subjects had normal levels of inflammatory markers C-reactive protein and IL-6. While the authors stated vitamin D levels had no effect on PASC symptoms, they pointed out that because the majority of subjects had normal levels, it is difficult to draw conclusions from this cohort. Ireland has a robust vitamin D fortification program, and the authors noted that very few of their PASC patients were hospitalized with severe illness. The authors also highlighted the majority of deficient subjects were non-caucasian, similar to data seen in myriad countries around the world. The study had a limited number of subjects, was not randomized, and was only four months long.

While the importance of nutrients and vitamin D levels for better outcomes for PASC patients will be debated until more data is revealed, the second category of single study literature that dominated for PASC concerned breathing therapies. Philip et. al (2022) performed a parallel-group, single-blind, randomized controlled trial at one of the United Kingdom's PASC clinics to evaluate patients with chronic breathlessness syndrome using a holistic breathing and wellbeing program called ENO Breathe over a 3 month period. ENO Breathe, through online video sessions, teaches breathing retraining with singing techniques and lullabies, as well as straw phonation techniques. The researchers screened 150 patients for lung function, echocardiography, and any other necessary imaging. Control group (74) took 6, once weekly, 1 hour sessions in a group setting taught by an ENO vocal specialist, while the other group (76) received standard care. Benefits were assessed based upon mental and physical health scores, as well as breathlessness test scores. ENO subjects exhibited mental health improvements and physical improvements compared to the standard care group. The researchers found a significant,

positive difference in breathlessness favoring the ENO group. Some in the ENO group reported better sleep quality and improvement in voice abnormalities. The authors noted that rehabilitative services for PASC are non-existent. This was the first randomized trial to offer some type of service, found to be safe and effective, that could complement standard care. Imperial College, where the clinic resides and the patients were evaluated, funded the study.

In addition, another English study by McNarry et. al (2022) explored the effect of breathing therapy for PASC. Also a randomized controlled trial, researchers assessed the efficacy of home-based therapy inspiratory muscle training (IMT) for PASC sufferers with chronic breathlessness syndrome for 8 weeks. The handheld inspiratory flow resistive device wirelessly syncs to mobile devices or computers through an app. The outcomes researchers were aiming for included health-related quality of life, psychological breathlessness and activities, chest symptoms, breathlessness indices, and maximal oxygen uptake ($\dot{V}O2max$). The IMT group exhibited improvements in health-related quality of life, psychological breathlessness and activities, inspiratory muscle strength, and VO2max versus the control group. Scores for chest symptoms and breathlessness indices showed no statistical differences between the IMT and control group. As was with the ENO program, this was the first randomized trial to assess IMT's efficacy. The limitations of the study was its small subject size, and of the 281 adults chosen, only 148 completed the study. There were also significantly more IMT (87) than standard care (37) subjects.

The third category of single study literature concerned aromatherapy. A randomized, double-blinded, placebo controlled clinical trial from Hawkins et. al (2022) evaluated the efficacy of an aromatherapy to increase energy in PASC patients. It must be stated that while the

trial was structured to the gold standard for research, the funding was provided by the manufacturer of the product used in the study. The authors focused on a primary symptom of PASC sufferers, fatigue. Their aim was to assess if an essential oil blend including thyme, orange peel, clove bud, and frankincense could increase energy in PASC sufferers for the short-term. Subjects were told to breathe 4 drops of a scent on a tester strip for 15 minutes every morning and evening for two weeks. Both groups were not told what scents were being put on the tester strips. The authors reported significantly lower fatigue scores and increased vigor when compared to the placebo group. Despite the encouraging results, there were drawbacks to the trial. The subject size was small (20 for each group) and even though women experience fatigue at much higher rates, there were only women and no men recruited in the trial. One subject had to stop the trial early because of recurring headaches. Even though their aim was to look at short-term increase in energy, a two week study is very short.

As cited in the introduction, there were numerous studies linking gut dysfunction with autoimmune disorders such as CFS, as well as PASC (Liu et. al, 2022). Thus, the question became what data existed for rebalancing gut microbiota from CAM therapies such as prebiotics and/or probiotics, and were they beneficial for PASC sufferers? This was the fourth category that dominated single study literature for PASC. Thomas et. al (2021) performed an experimental trial to address this question. The researchers administered a certified organic prebiotic (200 mg. inulin) and probiotic (10 Billion CFUs of Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactococcus lactis, Lactobacillus paracasei) supplement to 126 patients with post-COVID gut dysbiosis for 30 days to ascertain if their chronic gastrointestinal symptoms would improve. 82% percent of the subjects reported improved gastrointestinal

function, as well as improvements in fatigue, overall wellbeing, and cough. 1.5% reported bloating and diarrhea. The authors postulated that the supplement may improve gut-brain axis chronic inflammation through hormonal and neurotransmitter balance. While the subjects were in a hospital setting, the number of subjects was small and there was no randomized cohort.

Staying with gut integrity, the vagus nerve has been linked to gastrointestinal function. While one can argue that non-invasive vagus nerve stimulation (nVNS), a popular treatment for migraines, may not be considered a CAM therapy, for the purposes of this paper, it seems an alternative therapy that either alone or in conjunction with standard therapies may be helpful for PASC sufferers. Tornero et. al (2021) assessed the efficacy of non-invasive vagus nerve stimulation (nVNS) of 97 PASC patients. The subjects were randomized, controlled, and administered nVNS 3 times daily over a 5 day period. Researchers assessed serum C-reactive protein and procalcitonin markers before and after treatment. The treatment was very well tolerated. Subjects who received nVNS treatment showed significantly reduced C-reactive protein and procalcitonin levels than those who did not. The authors were not surprised by these findings as they cited nVNS efficacious for other chronic lung distress disorders. Moreover, because nVNS does not require a surgical implant, it is more easily administered. If larger trials concur, the authors suggested nVNS could be an ideal therapy for helping PASC sufferers. One major drawback of the study was that the nVNS manufacturer partially funded the study. Moreover, two authors listed were a consultant and employee of the nVNS manufacturer.

The final category that dominated single study literature for PASC study was Traditional Chinese Medicine (TCM). The Republic of China uses TCM preventatively, as well as a complementary treatment for patients with active COVID-19 infection. Less was known whether

TCM would assist with those suffering from PASC. A formula containing 16 herbs called Qingjin Yiqi granules (QJYQ) was given to 388 subjects along with respiratory training for 14 days to examine the effectiveness and safety of QJYQ . Pang et. al (2022) used a randomized, open-label clinical trial design, applying a modified Medical Research Council (mMRC) scale for breathlessness, and the Borg scale, a fatigue and exertion rating to two 194 subject groups. The primary endpoint (mMRC) showed remarkable improvements compared to the control group at 7 and 14 days. The secondary endpoint (Borg scale) showed a reduction compared to controls at days 7 and 14, but not as significantly as mMRC. However, in QJYQ subjects younger than 65 years, the secondary endpoint was considered remarkable. The authors noted that with some TCM, renal or liver issues are common. Although, the QJYQ group exhibited no differences in renal or liver function than the control group. The main drawback of the study was lack of placebo and double-blinding, as well as the short duration. While both groups performed respiratory training during the 14 days, the treatment was not solely focused on QJYQ.

To illustrate, after examining the data, it seemed that multiple CAM therapies used to support PASC may have promise for similar conditions such as CFS. In contrast, except for nutrients, there was very little data linking potential CAM therapies from conditions such as CFS to support PASC.

Discussion

The goal of this literature review is to examine the CAM approach to mitigate symptoms of PASC and similar diseases to PASC, such as CFS. From this review, the hope is that the results will elucidate which CAM therapies may be used beneficially to support not only PASC, but similar, deleterious autoimmune disorders such as CFS.

The findings support and highlight the use of specific CAM therapies for PASC, especially when no consensus for current therapies exist. While examining the use of CAM therapies for disorders such as CFS that are similar to PASC, there were results that hinted at benefits, especially from various nutrients (Bjørklund et. al, 2019 and Castro-Marrero et. al, 2021), but the studies were scant in number.

In contrast, while examining CAM therapies for PASC, key findings include the beneficial use of various nutrients to address deficiency and encourage faster recovery (Motti et. al 2022 and Hussein et. al, 2022). Herbs, aromatherapy, and TCM also seem to be viable CAM therapies to support recovery (Mukherjee et. al, 2022, Hawkins et. al, 2022 and Pang et. al, 2022). Addressing gut dysfunction with prebiotics and probiotics seem to play an integral role for supporting PASC sufferers, according to data revealed by Liu et. al, 2022. Furthermore, nVNS, a device used for migraine headaches, may be a viable option for PASC patients suffering from gut dysfunction and recently, a first-of-its-kind study found improvement in olfactory dysfunction, a common complaint for PASC sufferers (Vestito et. al, 2022). Another significant finding were the benefits of two forms of breathing therapy to ameliorate symptoms (Philip et. al, 2022 and McNarry et. al, 2022). Based upon the results of this review, when little or no therapies exist to help PASC sufferers, incorporating one or more of these CAM therapies when deemed appropriate for the individual, either integrated with standard therapy or as stand-alone therapies, may be warranted (Roth, Chan, and Jonas, 2021). Moreover, many of these CAM therapies may also support similar conditions to PASC such as CFS.

It must be noted that this review can only draw upon the last two years of research, because PASC did not exist until the COVID-19 pandemic. It was surprising that there was a

dearth of data showing the benefits of CAM for similar conditions to PASC, such as CFS and fibromyalgia. It seems the large numbers of people getting PASC created a sense of urgency for researchers to examine CAM therapies that could help PASC, at least much quicker than similar disorders have been studied. There was a noticeable theme that permeated throughout this review: the benefits of using CAM in lower economic areas. As data have shown, vaccinations for COVID-19 arrived later, if at all, and were utilized much less in impoverished areas than wealthier areas. It seems that lower income communities with citizens suffering from PASC would not have access to, or at least would be tardy in receiving necessary therapies to support PASC. In this review, Hussein et. al (2022), McNarry et. al (2022), Motti et. al (2022), Philip et. al (2022), and Roth, Chan, and Jonas (2021) highlighted the important role CAM therapies as either a first-line therapy or a bridge to standard therapy until it becomes available in low income communities. The authors suggest the CAM therapies examined are affordable and more accessible than expensive and less accessible medications and standard therapies.

It has been two years since PASC cases were found and no standard therapies are being used successfully to remit PASC. While the studies in this review all have flaws, whether small sample sizes, trial design flaws, conflicts of interest, among others, there are enough positive findings to consider incorporating certain CAM therapies to mitigate PASC. Moreover, there are specific guidelines that may be gleaned from these results that could be standardized anywhere in the world. Based upon this review, the National Institutes of Health should expand its very large grant, deemed necessary to find beneficial therapies for PASC, to include not just drug therapies, but CAM therapies as well. The NIH can use some of the results elucidated in this review to fund expanded studies for nutrients, herbs, aromatherapy, TCM, nVNS, and breathing therapy.

Given the limitations and pressures of the pandemic, it was encouraging to see what CAM studies were performed to support PASC. However, more studies need to be performed that include larger sample sizes. For example, the study performed by Hawkins et. al (2022) on aromatherapy included only 40 subjects total. Larger studies should lead to less examples of bias, as evidenced by the trial by Thomas et. al (2021), in which some of the authors were the creators of the probiotic formulation used in the study. There were conflicts of interest, such as the study by Tornero et. al (2021) that was funded by the manufacturer of the nVNS machines used in the trial. Some of the trials should be better designed so they can be accepted by the allopathic community, as evidenced by Hawkins et. al (2022) study, which only used female subjects. There needs to be more of a data consensus regarding how important it is to address nutrient deficiencies for PASC, as the conflicting results of the two vitamin D deficiency trials cited in this paper showed. Finally, research needs to expand upon existing CAM therapies that have not been investigated as of yet for PASC. When searching for data on CAM therapies for PASC and similar disorders for this paper, 15 different CAM therapies were included in the search, and only the few listed in this paper were substantive enough to explore.

Conclusion

The goal of this literature review was to examine the CAM approach to mitigate symptoms of PASC and similar diseases to PASC, such as CFS. From this review, the hope is that the results will elucidate which CAM therapies may be used beneficially to support not only PASC, but similar, deleterious autoimmune disorders such as CFS. Did this review bring clarity as to whether CAM had an impact on mitigating symptoms for PASC and similar autoimmune disorders? The data seemed to indicate that certain CAM therapies such as nutrients, prebiotics

and probiotics, herbs, aromatherapy, TCM, nVNS, and breathing therapy may mitigate symptoms of PASC and similar disorders, but more expansive research is necessary. As is often the case with CAM research because of lack of funding, the studies were small, funded by the product being researched, the trial structure was not always optimal, and bias creeped in. In addition, very few CAM therapies had been studied extensively. If any positive can be taken from a pandemic, in the case of CAM therapy, there was a sprouting of data in a very short time for ways to mitigate PASC symptoms, and in turn, similar disorders such as CFS and fibromyalgia. Before PASC, there was very little data on CAM therapies for disorders such as CFS and fibromyalgia. The existing evidence presented in this review will hopefully motivate researchers to not only expand upon existing research for CAM for PASC, but apply it to similar disorders such as CFS that affect millions around the world. Moreover, when at this time no consensus exists as to what therapies should be used for PASC, this review presented CAM as an affordable option for low income communities around the world.

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