

Clinical Trials on Alternative Medicines for COVID-19

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Abstract. In this study, we addressed the alternative medications that have been targeted in the clinical trials (CTs) to be evidenced as an adjuvant treatment against COVID-19. Based on the outcomes from CTs, we found that dietary supplements such as Lactoferrin, and Probiotics (as SivoMixx) can play a role enhancing the immunity thus can be used as prophylactics against COVID-19 infection. Vitamin D was proven as an effective adjuvant treatment against COVID-19, while Vitamin C role is uncertain and needs more investigation. Herbs such as Guduchi Ghan Vati can be used as prophylactic, while Resveratrol can be used to reduce the hospitalization risk of COVID-19 patients. On the contrary, there were no clinical improvements demonstrated when using Cannabidiol. This study is a part of a two-phase research study. In the first phase, we gathered evidence-based information on alternative therapeutics for COVID-19 that are under CT. In the second phase, we plan to build a mobile health application that will provide evidence based alternative therapy information to health consumers.

Keywords. Coronavirus; COVID-19; Alternative medicine; Clinical trial

1. Introduction

In the combat against COVID-19 outbreak, many FDA approved drugs have been used extensively [1]. Interestingly alternative medicines have gained a lot of attention during this pandemic in order to obtain safe, well-tolerated, cheap and available treatments without adverse side-effects. Many societies have a reasonable experience using herbs and traditional medication for diseases. Many traditional herbal medications and dietary supplements have been used against COVID-19 as they were known for their antiviral, anti-inflammatory and or immuno-boosting effects. In this study, we focused on exploring the clinical trials that evaluated this class of medication and discussed their clinical outcomes. This work is part of a two-phase research study. In the first phase, we gather evidence-based information on alternative therapeutics for COVID-19 that are under clinical trials (CT). In the second phase, we plan to build a mobile health application that will provide evidence based alternative therapy information to health consumers. The work presented in this study is part of the first phase of our proposed research study.

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2. Data Collection

We made reference to <https://clinicaltrials.gov> to populate the list of the ongoing CTs till 24 January, 2022 globally. Based on our analysis, in total, we found 40 CTs across the globe covering different types of alternative therapies. We categorized the trials according to the medication under evaluation. Each trial was explored to know the motivating hypotheses and the outcomes. We classified the alternative medicines under investigation by CTs into three groups: (a) dietary supplements, (b) vitamin and minerals, and (c) herbal medications (Table 1). The full list of the CTs and alternative medicines can be found at: https://github.com/tanviralambd/AltMed_COVID19.

Table 1. List of alternative medicines that are under clinical trials

Type	Name	Trial Number
Dietary Supplements	Lactoferrin, SivoMixx, Omega 3,	NCT04412395, NCT04427865, NCT04475120,
	Resistant Starch.	NCT04368351, NCT04495816, NCT04647604, NCT04342689
Vitamins and Minerals	Vitamin C, Vitamin D, Vitamin B, Vitamin Combinations, Selenium, Sodium Bicarbonate	NCT04395768, NCT04664010, NCT04356495,
		NCT04363840, NCT04482673, NCT04335084,
		NCT04386850, NCT04468139, NCT04525820,
		NCT04682574, NCT04401150, NCT04709744,
		NCT04411446, NCT04621058, NCT04489628, NCT04530448, NCT04655716, NCT04869579
Herbal	Cannabidiol, Guduchi Ghan Vati, Honey/Nigella, Huaier Granule, Kan Jang capsules, YinHu QingWen, Chinese preparation, Fuzheng Huayu, Resveratrol	NCT04615949, NCT04467918, NCT03944447,
		NCT04542876, NCT04480398, NCT04767087,
		NCT04553705, NCT04291053, NCT04847518,
		NCT04278963, NCT04310865, NCT04668222,
		NCT04279197, NCT04400890

3. Results

3.1 Dietary Supplements

Lactoferrin: In Egypt, two CTs related to Lactoferrin are going on. The first one; NCT04412395; is evaluating Lactoferrin as a potential treatment against COVID-19 infection. The second one; NCT04427865, addresses the safety of healthcare providers by testing Lactoferrin as a preventive therapy against COVID-19. The primary outcome of this study is based on the incidence of the COVID-19 infection.

SivoMixx: It is a probiotic which contains a mixture of lactic acid bacteria. The benefit of this medication is to restore the gut microbiota which has been altered using antibiotics, the dietary changes and the inflammatory reactions caused by COVID-19 infection [2]. A CT is being held in Italy, NCT04368351, to evaluate the effectiveness of SivoMixx as a probiotic in reducing the acute diarrhea resulting from COVID-19. The disappearance of the acute diarrhea is considered as a primary outcome of this study.

Omega 3 oil: Omega 3 fatty acid was claimed to play a great role in the immune-modulating system and boosting the antiviral mechanism. A CT, NCT04495816, is being held in the US to investigate the role of Omega 3 in treating post COVID-19 anosmia and olfactory dysfunction. Another CT, NCT04647604, aims to assess the role of Omega 3 in resolving the inflammatory storm in COVID-19 patients.

Resistant Starch: A CT, NCT04342689, is ongoing in the US to investigate the role of Resistant Starch in COVID-19 treatment, to estimate the rate of hospitalization.

3.2 Vitamins and Minerals

Vitamins: Possessing antiviral, antioxidant, anti-inflammatory and immunomodulatory characteristics, Vitamin C can be considered as a potential therapeutic treatment against COVID-19. It is evaluated in multiple CTs, such as NCT04395768 and NCT04664010. One CT, NCT04682574, is ongoing in Saudi Arabia for estimating the recovery duration, addressing the effect of Vitamin C, but combined with Zinc, Quercetin and Bromelain on the clinical outcomes of COVID-19 patients. A CT, NCT04363840, is taking place in the US to check the role of Vitamin D with Aspirin. Another study, NCT04482673 in the US, is focusing on Vitamin D supplementation for the mitigation and prevention of COVID-19 infection, and considers the blood level of Vitamin D in COVID-19 negative participants and positive participants as a primary outcome. Another CT, NCT04335084, is taking place in the US for the effectiveness of the combination of Hydroxychloroquine, Zinc, Vitamin C and Vitamin D in COVID-19 prevention.

Minerals: Based on its anti-oxidative, immune-modulating and anticoagulant effects and on the claims that Selenium deficiency may be linked to mortality risk in COVID-19 infection, a US CT, NCT04869579, is ongoing to investigate any potential role for Selenium in the treatment against COVID-19. Sodium Bicarbonate has a suggested role in treating pneumonia associated with COVID-19 infection, as it has anti-influenza properties. Sodium Bicarbonate is being evaluated by an ongoing CT, NCT04374591, for evaluating the cough relief and the return of the body temperature to normal. Under NCT04655716 and NCT04530448, investigators are exploring the role of Sodium Bicarbonate in urine alkalinization to prevent acute kidney injury from COVID-19.

3.3 Herbal Medications

Cannabis and Cannabidiol: Cannabidiol, one of the Cannabis constituents, can block SARS-CoV-2 virus entry to the cell by downregulating ACE2 enzymes [3]. NCT03944447 is inquiring about the ability of Cannabis in inhibiting the virus entry, for the prevention of COVID-19. Other two CTs, NCT04615949 and NCT04467918, are evaluating the role of Cannabidiol in reducing the severity of COVID-19 infection.

Guduchi Ghan Vati: It is an herbal preparation which is extracted from Guduchi (*Tinospora cordifolia* Miers) stem, found in India. It has anti-inflammatory, antiallergic and immunomodulatory properties. The features exhibited by this plant were thought to be beneficial against COVID-19 infection. In India, there are two CTs, NCT04542876 and NCT04480398, that are evaluating its efficacy in asymptomatic COVID-19 patients.

Nigella Sativa: The anti-inflammatory and immune-boosting effects *Nigella Sativa* [4], are being investigated in Pakistan by a CT (NCT04767087). The participants will receive *Nigella* mixed with honey and distilled water. The primary outcome is measured by counting the days to have the negative result for COVID-19 PCR. Another CT (NCT04553705) held in Egypt, aims to evaluate the clinical significance of Black Seed, but with other herbs like Anise seed, Licorice extract, Indian cactus and Omega 3 oil.

Resveratrol: It is a polyphenol which is found in some edible natural resources mainly grapes and peanuts. It exhibits antiviral effect, among many other beneficial effects, inhibiting viral replication. These features nominated it as a potential adjuvant treatment against COVID-19. NCT04400890 is a clinical study that is proposed in the US to explore the effectiveness and evaluate the safety of Resveratrol in COVID-19 patients for estimating the hospitalization rates.

KAN-JANG: It is an herbal medication that is used against common cold and upper respiratory tract infection, in some European countries. The primary outcome of this study is based on estimating the duration of the symptoms.

Chinese Medicine: Huaier Granule is a traditional Chinese medicine, which consists of aqueous extract of *Trametes robiniophila murr* in the form of granules. A Chinese CT, NCT04291053, is established to inquire about the safety and efficacy against COVID-19. Yinhu Qingwen is another Chinese herbal medicine which is used as antiviral, as mentioned in CTs NCT04278963 and NCT04310865. The primary outcomes are the mean recovery time of the patients and the ratio of the oxygenated index of the arterial blood, respectively. Fuzheng Huayu is another Chinese herbal complex mixture that contains an antifibrotic substance which is used to treat pulmonary fibrosis resulting from COVID-19 infection.

4. Clinical Outcomes from the Trials, Limitation and Future Works

Only three studies (NCT04368351, NCT04400890, NCT04467918) out of 40 have its results released in indexed publications. The results are promising for some therapies (e.g., SivoMixx and Resveratrol) but not promising for others (e.g., Cannabidiol). Probiotics, such as SivoMixx, have a promising role in enhancing the immunity status of the patients [5]. Given its anti-viral, antioxidant and anti-inflammatory effects, Resveratrol can be an effective adjunct treatment [6]. At the given doses in the study, NCT04467918, Cannabidiol did not enhance the clinical symptoms and failed to alter the prognosis of COVID-19 infection [7].

Our study has some limitations that need to be mentioned. We included CT registered only under <https://clinicaltrials.gov> databases. Many CTs have not issued the results yet, and many CTs have been either terminated, suspended, or withdrawn. This has limited our discussion about the validity of these medications in regards with COVID-19 treatment, in terms of safety or efficacy. In future, we will build a mobile health application to provide evidence-based alternative therapy information for COVID-19.

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