




# Alternative therapies for viral infections caused by SARS-Cov-2

*Terapias alternativas para infecções virais causadas pelo SARS-Cov-2*

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## Abstract

**Introduction:** The relevance of the studied topic lies in the complexity of the treatment of infection caused by SARS-CoV-2. **Objective:** To discuss the potential advantages and disadvantages of alternative treatments compared to conventional medical approaches, and to highlight the importance of collaborative communication between patients and healthcare providers in making informed decisions about alternative treatments of the SARS-CoV-2 virus. **Methods:** The research methodology employed literature analysis methods, including bibliographic and bibliosemantic approaches. The study used theoretical, systematic, and statistical methods, including analysis, synthesis, generalization, interpretation, classification, and meta-analysis to explore alternative treatments for SARS-CoV-2 infections, their interrelationships, and statistical trends in incidence. **Results:** The study identifies diverse alternative therapies for treating SARS-CoV-2 infections, highlighting herbal medicine, acupuncture, reflexology, biohacking, homoeopathy, and magnetotherapy. It underscores the potential benefits of herbal remedies like garlic, ginger, chamomile, and honeysuckle, as well as vitamins (C, D, B12) and minerals (zinc, selenium) in managing COVID-19 symptoms. **Conclusion:** While offering holistic benefits, these therapies warrant cautious consideration due to limited scientific backing and potential interactions. Cultural understanding, patient-provider dialogue, and informed choices are key in harnessing the potential of alternative medicine alongside conventional approaches for managing COVID-19 challenges.

**Keywords:** Alternative medicine. Coronavirus infection. Herbal medicine. Treatment effectiveness. Resistance.

## Resumo

**Introdução:** A relevância do tema estudado reside na complexidade do tratamento da infecção causada pelo SARS-CoV-2.

**Objetivo:** Discutir as potenciais vantagens e desvantagens dos tratamentos alternativos em comparação com as abordagens médicas convencionais e realçar a importância da comunicação colaborativa entre os doentes e os prestadores de cuidados de saúde na tomada de decisões informadas sobre os tratamentos alternativos do vírus SARS-CoV-2. **Métodos:** A metodologia de investigação utilizou métodos de análise da literatura, incluindo abordagens bibliográficas e bibliosemânticas. O estudo utilizou métodos teóricos, sistemáticos e estatísticos, incluindo análise, síntese, generalização, interpretação, classificação e meta-análise para explorar tratamentos alternativos para as infecções por SARS-CoV-2, suas inter-relações e tendências estatísticas da incidência. **Resultados:** O estudo identifica diversas terapias alternativas para o tratamento das infecções por SARS-CoV-2, destacando a fitoterapia, a acupuntura, a reflexologia, o biohacking, a homeopatia e a magnetoterapia. Sublinha os potenciais benefícios dos remédios à base de plantas como o alho, o gengibre, a camomila e a madressilva, bem como das vitaminas (C, D, B12) e dos minerais (zinco, selênio) na gestão dos sintomas da COVID-19. **Conclusão:** Embora ofereçam benefícios holísticos, estas terapias devem ser consideradas com cautela devido ao apoio científico limitado e às potenciais interações. A compreensão cultural, o diálogo paciente-provedor e as escolhas informadas são fundamentais para aproveitar o potencial da medicina alternativa juntamente às abordagens convencionais para gerir os desafios da COVID-19.

**Palavras-chave:** Medicina alternativa. Infecção por coronavírus. Fitoterapia. Eficácia do tratamento. Resistência.

## Introduction

The year of 2019 was a year of great challenges for one of the largest pandemics in human history: the coronavirus infection. According to the statistics reported at the beginning of the epidemic, China, Italy, the United Kingdom, and others had the highest mortality and morbidity rates.<sup>1</sup> In September 2022, despite the introduction of a vaccine against coronavirus, the highest incidence rates were in the United States, India, and Brazil.<sup>2</sup> SARS-CoV-2 also affected Poland, Albania, Ukraine, Armenia, and Kazakhstan, and caused countless deaths.

During the last years of the pandemic, medical science and technology appeared to have advanced rapidly, suggesting the possibility of inventing a cure for SARS-CoV-2.<sup>3</sup> The development and deployment of vaccines have been a major step forward. These vaccines, although not entirely preventing infection, have been crucial in reducing the severity of the disease and the rates of hospitalization and death. The effectiveness of vaccines varies, and they may be less effective against certain variants of the virus, but their role in controlling the pandemic has been indispensable.

However, there is still no effective drug or therapeutic regimen for the treatment of coronavirus infection. As of today, doctors use the method of adjusting a set of medications to suit the individual case. That is precisely why this issue is extremely relevant not only in a pandemic but also in the context of antibiotic resistance.<sup>4</sup> Admittedly, today the attention of modern scientists is drawn to the general clinical picture of coronavirus infection. Nevertheless, the treatment of this disease does not exclude the treatment of other diseases, presumably due to the specifics of the pathogenesis of the latter. This leads to a distortion of the clinical picture and, accordingly, ineffective therapy. In other cases, SARS-Cov-2 complicates the course of concomitant pathology, including viral diseases.<sup>5</sup>

Mutual and complementary treatments in the form of alternative methods offer a wide range of benefits. Referring to reputable scientists such as Soileymani et al.,<sup>6</sup> phytotherapy (herbal medicine) can be considered one of the most commonly used in the treatment of a wide variety of complex pathological conditions. According to the World Health Organisation (WHO), 80% of the population of developing countries rely on conventional medicine or the care to which a particular person is accustomed. At this time, many are unaware of the possibility of using methods like reflexology, apitherapy, or herbal medicine, and thereby undermining the value of natural medicines and their derivatives.<sup>7</sup> Common people and prominent medical researchers mostly focus on medications of chemical origin, but which have antiviral properties (against the human immunodeficiency virus - HIV, SARS, MERS, influenza, etc.), and also turn to immunostimulants for disease prevention.<sup>8</sup>

Bijelić et al.<sup>9</sup> suggested some important remarks regarding the phytotherapeutic features of plants. In particular, the authors emphasise the significance of

herbal medicines as antiviral agents. Although such treatment as an independent therapy may not have a great effect, as a supplement to traditional treatment, it demonstrates considerable efficiency. These plants include: all legumes (peas, beans, etc.), *Curcuma domestica*, *Glycyrrhiza glabra*, *Artemisia annua*, *Scutellaria baicalensis* or *Lamium*, *Lycoris radiata*, and others.<sup>10</sup> The authors conclude that phytochemicals offer advantages over conventional drugs due to their historical use and perceived natural status, but challenges such as low bioavailability necessitate further pharmaceutical research for optimal formulation. More extensive and rigorous clinical studies on larger patient populations are needed to draw more definitive conclusions and validate these natural agents' effectiveness against the virus.<sup>9</sup>

Meanwhile, Han et al.,<sup>11</sup> in their research, demonstrate the effectiveness of acupuncture on people with SARS-CoV-2. During data processing, two compounds with the highest activity and more than 180 targets of protein origin were identified. This fact suggests that this may be related to the effect of acupuncture and the treatment of infectious diseases, which is based on the suppression of inflammatory stress, stabilisation of immune processes, and regulation of nervous system function. In this case, changes occur even at the level of activation of the neuroactive interaction of ligand receptors and calcium signalling pathways.

Moreover, it was found that the condition of people with infections caused by SARS-CoV-2 is associated with carcinogenesis.<sup>11</sup> The above studies have proven that acupuncture has an advantageous effect against both coronavirus disease and the complications caused by the virus.<sup>6,9,11</sup> This method also has a significant range of benefits in the treatment of other infectious conditions that occur with SARS-CoV-2, including for people suffering from cancer, cardiovascular disease, and conditions accompanied by *Staphylococcus aureus* infection.<sup>11</sup>

The purpose of this study is to explore and analyze the potential benefits and drawbacks of using various alternative therapies for the prevention and treatment of SARS-CoV-2 infections. The scientific data on different types of alternative treatments for SARS-CoV-2 infection was summarised. The study seeks to substantiate whether or not the use of alternative therapies such as acupuncture, homoeopathy, biohacking, and reflexology is rational. The authors analyse naturopathy as the most developed area of alternative medicine.

The effectiveness of each of the presented treatment methods is determined and their main advantages and disadvantages are highlighted.

## Methods

To achieve the set objective, the main methods of literature analysis were used: bibliographic and bibliosemantic methods. The latter involved studying and reviewing the latest specialised international literature on the issue under study. This was accomplished by analysing scientometric databases such as Web of Science, Scopus, Google Scholar, and PubMed over four years (i.e., from March 2020 to April 2023). The article analyses literature sources devoted to the study of the pathogenesis, diagnosis and treatment of infection caused by SARS-CoV-2. Scientific sources on complications of coronavirus infection, as well as other infectious diseases that arise as a result of SARS-CoV-2 infection, were reviewed. The following terms, phrases, and keywords were used to search for relevant data in scientometric databases: "SARS-CoV-2", "coronavirus", "pandemic", "treatment", "alternative treatment", "complementary therapy", "Chinese medicine", "herbal medicine", "rehabilitation", "post-COVID syndrome", "acupuncture", "immunogenesis of coronavirus infection", "TV rehabilitation". Other keywords were plant names and combinations of vitamins and macronutrients: all legumes (peas, beans, etc.), ascorbic acid, zinc, selenium, vitamin B2, B3, B6, B12, *Curcuma domestica*, *Glycyrrhiza glabra*, *Artemisia annua*, *Scutellaria baicalensis* or *Lamium*, *Lycoris radiata*, etc.

The analysis focuses on alternative methods of treating respiratory syndrome in coronavirus infection, the risks of infection in patients with SARS-CoV-2 with other types of viruses, such as influenza virus, papillomavirus, herpes, and human immunodeficiency virus, and alternative methods of combating them. This paper uses the following research methods: theoretical and systematic methods of cognition. The issue addressed required the use of methods of analysis, synthesis, generalisation, explanation, and classification. The method of analysis involved collecting data and breaking down the main content into theses. The synthesis was used to display alternative treatments for SARS-CoV-2 infections as an integrated entity and its interrelationships.

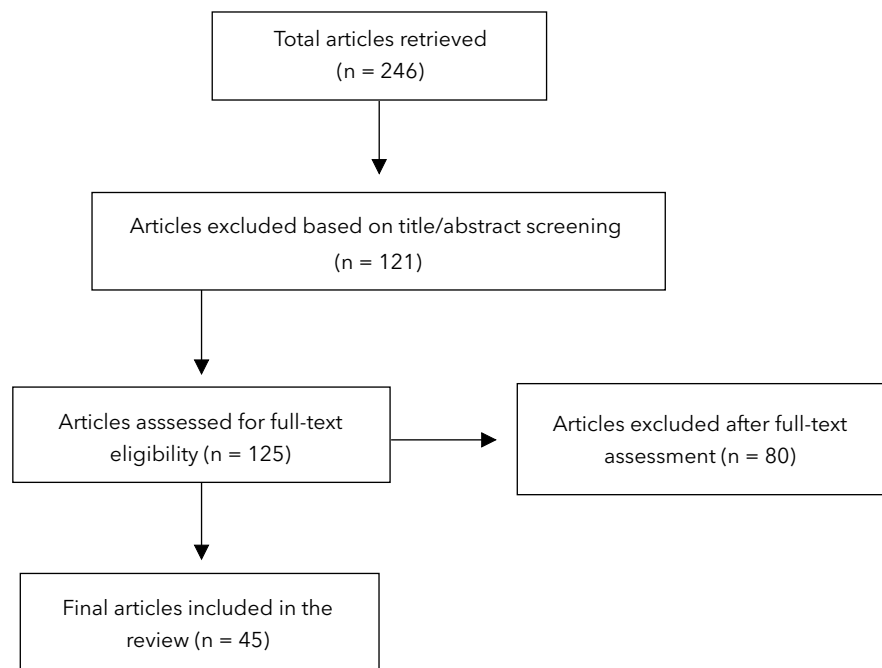
The method of data generalisation was used to describe the main common features of each treatment. The authors use the method of interpretation to characterise the main concepts and provisions of complementary and alternative treatment as concepts that have common and distinctive features. The classification method provides detailed information on the breakdown of alternative treatments to facilitate the interpretation of each type of therapy. It is worth noting that the empirical method is closely related to other methods and represents the above methods of generalisation and classification.

The comparative method combines most of the properties of the above-mentioned research methods to accurately characterise the SARS-CoV-2 virus, the symptom complex, infectious diseases it causes as a result of infection, complications, and known methods of alternative medicine. The statistical method of the study was used in two interrelated areas: as one of the methods of analysing and processing scientific sources, as well as for a general representation of the scope and variation of the incidence of SARS-CoV-2 infection.

Meta-analysis as a type of statistical analysis is used to analyse the presented set of sources on the subject with a possible error of judgment. Nevertheless, this method provides a basis for determining an average assessment or judgment regarding the goal and the currently unresolved issues related to alternative medicine in the treatment of SARS-CoV-2 infection.

## Results

The initial database search retrieved 246 articles (67 from PubMed, 56 from Scopus, 44 from Web of Science, 79 from Google Scholar). After title and abstract screening, 121 articles were excluded (63 not relevant to the topic, 18 in vitro studies, 23 animal studies, 17 reviews/commentaries). The remaining 125 articles underwent full-text review, following which 80 were further excluded (53 did not meet inclusion criteria, 14 had insufficient data, 13 had duplicate data). Finally, 45 articles were chosen to be read in full (Figure 1). Twenty-nine articles were included in the systematic review (Table 1).



**Figure 1** - Flowchart depicting the process of identifying, evaluating, excluding, and including studies.

**Table 1** - Studies selected to integrate the systematic review

Article	Design/Sample	Mechanisms/Results
Soileymani et al. <sup>6</sup>	This narrative review employed a comprehensive search strategy in PubMed, Scopus, and Google Scholar databases, spanning various types of studies in medicine, pharmacology, toxicology.	This review underscores the potential of natural resources and medicinal herbs as sources for new drug discovery in the prevention and treatment of COVID-19, outlining mechanisms such as immune boosting, hand hygiene, virus binding and entry inhibition, virus replication inhibition, and host-directed therapies, while emphasizing the need for further research to validate these strategies in the fight against the pandemic.
Bijelić et al. <sup>9</sup>	This research employed in vitro and in vivo studies on phytochemicals in the context of COVID-19, up until September 2022, with a brief mention of complementary data from preclinical studies.	Currently, promising natural agents for COVID-19 treatment include quercetin, glycyrrhizin, resveratrol, kaempferol, and thymoquinone, with the advantage of generally low side effects associated with natural products, though bioavailability challenges warrant further pharmaceutical technology research for effective drug formulation.
Han et al. <sup>11</sup>	The study utilized a systematic search approach across 6 databases up to December 31, 2020, with specific search terms related to COVID-19, respiratory symptoms, inflammation, and acupuncture techniques to gather relevant data.	The study's bioinformatics and network topology analysis revealed that acupuncture for COVID-19 primarily operates through anti-inflammatory mechanisms, immune system activation, and nervous system modulation, suggesting its potential effectiveness against COVID-19 symptoms and potential additional benefits for patients with cancer, obesity, and cardiovascular disease, but emphasizes the need for further rigorous clinical and basic research for confirmation.
Kladar et al. <sup>12</sup>	This prospective cross-sectional study utilized a specially created online survey, hosted on the web page, focusing on sociodemographic characteristics, COVID-19 experiences, therapy with conventional drugs, phytotherapy, dietary supplements, and special diets among participants in the context of the COVID-19 pandemic in the investigated region.	The study findings indicate that the use of medicinal plants as a form of therapy against COVID-19 is widely adopted and perceived as effective and safe, particularly due to its presumed positive impact on the respiratory and immune systems, emphasizing the importance of using high-quality, recognized products, and consulting with medical professionals for optimal benefits.
Li et al. <sup>13</sup>	The study design involved the screening of active components and targets of honeysuckle using the Traditional Chinese Medicine Database and Analysis Platform (TCMSP), predicting pharmacokinetics with SwissADME and pkCSM databases, collecting mild COVID-19 transcriptome data from the Gene Expression Omnibus (GEO) database, and utilizing various bioinformatics tools.	The analysis revealed that seven active ingredients in honeysuckle demonstrated favorable oral absorption and medicinal properties, and both the targets of these active ingredients and differentially expressed genes in mild COVID-19 were significantly associated with immune signaling pathways, particularly showing statistical significance in the expressions of RELA and MAP3K7.
Al-Kuraishy et al. <sup>19</sup>	This review critically examines the potential therapeutic role of Ginkgo biloba L. folium extract (EGb) in managing COVID-19, focusing on its anti-inflammatory and antioxidant properties, its mechanisms of action against SARS-CoV-2, and the possibility of utilizing nanosystems for targeted delivery and enhanced efficacy in phytotherapy.	The review highlights that Ginkgo biloba L. folium extract (EGb) may have a potential role in managing COVID-19 by exerting its antiviral effects through mechanisms such as inhibiting the SARS-CoV-2 3-chymotrypsin-like protease, and by mitigating pulmonary inflammatory disorders, including reducing neutrophil elastase activity, proinflammatory cytokine release, platelet aggregation, and thrombosis, suggesting its potential as an adjuvant therapy for COVID-19.
Muscogiuri et al. <sup>29</sup>	This study involved 500 participants, comprising 250 males and 250 females, whose body composition was assessed using bioelectrical impedance analysis, and serum 25OHD concentrations were measured via chemiluminescence immunoassay.	The study found that serum 25OH vitamin D (25OHD) concentrations were consistently higher in males compared to females across all body mass index (BMI) categories, with a significant decrease in 25OHD concentrations as BMI values increased.
Paudyal et al. <sup>10</sup>	This narrative commentary addresses the increased demand for complementary and alternative medicines (CAM) during the COVID-19 pandemic and aims to inform healthcare professionals, including pharmacists, about current global practices, policies, research, patient behaviors, and cultural considerations related to CAM use in COVID-19, with a focus on different continents and regions historically associated with diverse CAM practices.	The use of complementary and alternative medicines (CAM) in COVID-19 is widespread and influenced by geographical, cultural, and religious factors, with herbal products often perceived as effective for symptom relief and treatment, despite limited human clinical trial data supporting their efficacy.

**Table 1** - Studies selected to integrate the systematic review (continued)

Article	Design/Sample	Mechanisms/Results
Ang et al. <sup>14</sup>	This study conducted a systematic review of 21 systematic reviews (SRs) analyzing the efficacy of herbal medications for treating COVID-19, using a search of four databases up to October 20, 2021, and assessed the methodological quality of these SRs using the AMSTAR 2 tool.	Although there is a substantial body of evidence suggesting potential benefits, the overall quality of the evidence remains insufficient to make definitive judgments about the effectiveness of herbal medicine therapies, emphasizing the importance of upholding methodological standards in clinical studies and SRs, even in the context of the pandemic.
Fiorino et al. <sup>15</sup>	The authors conducted a comprehensive search for reviews describing the characteristics of autoimmune diseases, therapeutic protocols for their treatment, and studies investigating the potential efficacy of vitamins A, D, E, and C in enhancing immune system function, aiming to identify common pathogenetic mechanisms between autoimmune diseases and SARS-CoV-2 infection.	SARS-CoV-2 infection triggers a dysregulated immune response characterized by intense proinflammation leading to cytokine release syndrome (CRS) and acute respiratory syndrome (ARDS), particularly in older individuals, and this review explores the potential of vitamins A, D, E, and C to modulate the immune response, shifting it away from a proinflammatory Th17-mediated profile seen in autoimmune diseases towards a T-cell regulatory phenotype, suggesting a therapeutic role for these micronutrients in restoring normal antiviral immune function and potentially mitigating SARS-CoV-2 infection's severity.
Paul et al. <sup>17</sup>	The authors used hydrogels with varying elastic moduli and conventional tissue culture surfaces to investigate the impact of lung parenchymal tissue stiffness on SARS-CoV-2 infection rates in lung epithelial cells challenged with Spike (S) protein pseudotyped lentiviruses.	The study found that cells on softer and sparser scaffolds, resembling the biomechanical properties of younger lungs, exhibited higher infection rates by both the native SARS-CoV-2 strain and the D614G variant, suggesting that age-related changes in lung biomechanics may not increase susceptibility to SARS-CoV-2 infection, implying that other factors, such as weakened immunity, may contribute to the heightened disease burden observed in older individuals during the pandemic.
Abdelgawad et al. <sup>18</sup>	This study reviewed recent research to identify olive leaves as a potential co-therapy supplement for the treatment and improvement of clinical manifestations in COVID-19 patients.	The review highlighted that olive leaves, rich in phenolic compounds and triterpenoids with reported anti-SARS-CoV-2 properties, along with their established in vivo anti-inflammatory, analgesic, antipyretic, immunomodulatory, and antithrombotic activities, have the potential to be a co-therapy supplement for the treatment of COVID-19 and its associated symptoms, particularly in controlling the inflammatory cytokine storm and disseminated intravascular coagulation in patients.
Pranskuniene et al. <sup>20</sup>	The survey was conducted using the deep interview method. The respondents mentioned 60 species of medicinal plants from 29 different families used for the treatment and prevention of respiratory system disorders (for cough mostly, 51.70% of all indications).	The study found that during the COVID-19 pandemic in the Pasvalys district of Lithuania, herbal medicines were commonly used for the treatment and prevention of respiratory system disorders, primarily for cough, with 60 species of medicinal plants mentioned, but a significant proportion of these plants were not included in European Medicines Agency monographs, indicating potential safety concerns and the need for adherence to safety guidelines when considering herbal remedies for COVID-19 symptoms.
Holford et al. <sup>24</sup>	The literature review aimed to investigate the potential therapeutic benefits of vitamin C in the prevention and treatment of respiratory infections, including COVID-19, through both oral and intravenous administration, with a focus on its impact on reducing infection incidence, duration, and severity.	Vitamin C, due to its antioxidant, anti-inflammatory, and immunomodulating effects, may have potential therapeutic benefits in preventing and ameliorating COVID-19 infection, particularly when administered orally or intravenously in certain doses, by reducing the incidence and duration of respiratory infections and improving outcomes, including reduced mortality and hospital stays in severe cases, warranting further clinical trials.
Feyaerts et al. <sup>25</sup>	This article discusses the potential use of vitamin C, both as prophylaxis at a relatively low dose and as an intravenous high-dose regimen for severe COVID-19 cases, based on evidence of its ability to reduce mediators like interleukin-6 and endothelin-1.	The authors suggest that elevated levels of mediators like interleukin-6 and endothelin-1 in severe COVID-19 cases may contribute to the disease's characteristics, and there is evidence that high doses of vitamin C can reduce these mediators, supporting the potential benefit of using vitamin C at low doses for prophylaxis and high doses for severe COVID-19 cases.

**Table 1** - Studies selected to integrate the systematic review (continued)

Article	Design/Sample	Mechanisms/Results
Ahmad et al. <sup>26</sup>	The study investigates the potential applications of vitamin C as a prevention and treatment for COVID-19, focusing on its immune-modulatory mechanisms, antioxidant properties, and its potential to reduce oxidative damage and mitigate cytokine attacks.	The study suggests that vitamin C exhibits antioxidant and antiviral effects, making it a promising option for combating SARS-CoV-2 infections, but emphasizes the need for further research, including randomized controlled trials (RCTs) and large cohort studies, to confirm its effectiveness, especially in combination with other drugs, intravenous administration, and for critically ill patients.
Hui et al. <sup>27</sup>	The authors used genetic tools derived from a genome-wide association study (GWAS) of plasma vitamin C levels in a sample of 52,018 people of European ancestry selected on the basis of an F-statistic > 10 as strong tools.	Genetically predicted circulating levels of vitamin C were not found to be associated with the susceptibility to severe COVID-19, COVID-19 hospitalization, any COVID-19 infection, or pneumonia, suggesting limited support for the use of vitamin C in the prevention and treatment of these conditions through these pathways, unless high-dose vitamin C infusion operates through distinct biological mechanisms.
Barrea et al. <sup>28</sup>	In this review, data were summarized using a narrative approach, drawing from clinical expertise and interpretation of available evidence in peer-reviewed journal literature. PubMed and Google Scholar were searched using relevant terms including COVID-19, long COVID-19, mechanisms, risk, SARS-CoV-2, symptoms, and vitamin D.	The COVID-19 pandemic has seen rising cases and lingering symptoms among patients, particularly those with long-term sequelae, and vitamin D deficiency has been associated with increased severity and mortality in COVID-19 cases, highlighting its immunomodulatory role and potential as a cost-effective and safe supplement in COVID-19 treatment.
Subramanian et al. <sup>30</sup>	This is a narrative review but informed by a PubMed literature search that included as search terms 'COVID-19 and vitamin D' and with emphasis on reports published since January 2021.	The evidence for the impact of vitamin D deficiency on COVID-19 risk and severity is largely indirect, and future studies should consider the dose and formulation of vitamin D, with calcifediol potentially being more effective for both prevention and treatment of acute respiratory infections, while regular low-dose daily supplementation to prevent deficiency should be encouraged.
Shakoor et al. <sup>31</sup>	A total of 35 relevant studies specifically on COVID-19 and nutrition or diet components were identified.	The potential benefits of vitamins C, D, E, zinc, selenium, and omega-3 fatty acids in supporting the immune system and COVID-19 patients, particularly in the elderly population, are discussed, and higher dosages of vitamins D, C, and zinc are suggested for possible positive effects during COVID-19 infection, although clinical trials are needed to confirm their effectiveness in COVID-19 patients, along with the exploration of other immunomodulatory micronutrients like vitamin B.
Varikasuvu et al. <sup>32</sup>	A total of 6 RCTs with 551 COVID-19 patients were included.	The overall collective evidence pooling all the outcomes across all RCTs indicated the beneficial use of vitamin D intervention in COVID-19 (relative risk, RR = 0.60, 95% CI 0.40 to 0.92, Z = 2.33, p = 0.02, I <sup>2</sup> = 48%). Conclusively, COVID-19 patients supplemented with vitamin D are more likely to demonstrate fewer rates of ICU admission, mortality events, and RT-PCR positivity.
Tabatabaeizadeh et al. <sup>36</sup>	A systematic search has conducted for manuscripts through PUBMED/Medline and Google Scholar up to September 2021. Based on the heterogeneity a fixed-effect or random-effect model, the OR and 95% CI were used to assess the combined risk.	After assessment, five studies with 1506 participants in case and control groups were included in meta-analysis. The OR for one study was not estimable, and the pool OR was estimated for other studies with 1398 participants. The meta-analysis showed that zinc supplementation in cases led to a significant lower risk of mortality when it was compared with the control group; pooled OR (95% CI) was 0.57 [0.43, 0.77] (P < 0.001).
Borges et al. <sup>37</sup>	The review included peer-reviewed randomized controlled trials (RCTs) and observational studies in any language that assessed COVID-19 patients treated with melatonin, zinc, or vitamin C.	The review highlights that while nutritional supplementation with melatonin, zinc, and vitamin C is often cost-effective and associated with anti-inflammatory and antioxidative properties, most randomized controlled trials (RCTs) involving these supplements for COVID-19 are still in development, with inconclusive data from relatively small sample sizes and early terminations of trials.

**Table 1** - Studies selected to integrate the systematic review (continued)

Article	Design/Sample	Mechanisms/Results
Boretti <sup>40</sup>	The manuscript proposes a statistical analysis of the works with Zn for COVID-19 infection.	The review of Zinc (Zn) supplementation for COVID-19 infection indicates that Zn supplementation may reduce the risks of serious outcomes from COVID-19 infection, particularly when taken in conjunction with antiviral drugs, with a range of risk reduction from 37% in late treatment to 78% in sufficiency.
Pisoschi et al. <sup>41</sup>	This review synthesizes existing literature to discuss the potential roles of vitamins in reducing oxidative stress, countering cytokine storms, and their direct antiviral activities in the context of viral infections, including SARS-CoV-2, with a focus on timing, dosage, and potential interactions among these micronutrients.	This review highlights the role of antioxidants, including vitamins, in mitigating oxidative stress, reducing cytokine storms, and potentially exerting direct antiviral effects in viral infections such as SARS-CoV-2, emphasizing their ability to lower oxidative stress markers, alleviate cytokine storms, and potentially reduce disease severity by modulating pro-inflammatory cytokines and countering hyperinflammation.
Alshammari et al. <sup>42</sup>	This review examines clinical studies, compositions, and patent literature related to selenium's potential in preventing and treating COVID-19, focusing on its mechanisms of action and the development of selenium-based compositions and dosage forms for COVID-19 management.	Clinical studies and patent literature suggest that selenium monotherapy and its combinations with various nutritional supplements and drugs could be effective in COVID-19 management, emphasizing a correlation between COVID-19 and selenium deficiency, which opens avenues for novel selenium-based compositions and dosage forms for COVID-19 treatment, while recognizing the importance of considering selenium's narrow therapeutic window and chemical interactions in formulation.
Rayman et al. <sup>43</sup>	In this review, the association between selenium (Se) status and COVID-19 outcomes were investigated based on available data and serum samples from COVID-19 patients in Chinese cities with varying Se statuses.	The review highlights the historical significance of selenium (Se) in reducing the severity of viral infections and presents evidence of a significant association between COVID-19 cure rates and background Se status in Chinese cities, suggesting additional mechanisms beyond selenoprotein optimization.
Darand et al. <sup>44</sup>	This study analyzed data from 9189 adult participants aged 20 to 69 years from the Yazd Health Study (YaHS) and Taghzieh Mardom-e-Yazd (TAMIZ) study, utilizing a validated FFQ to assess dietary intakes, and employed multivariable logistic regression analysis.	The study found that higher dietary intake of vitamin B5 was associated with a 47% reduction in the odds of COVID-19, and moderate intake of vitamin B12 was linked to a protective effect against COVID-19, while no significant associations were observed for dietary intake of vitamin B1, B2, B3, B9, and B-complex in relation to COVID-19 incidence.
Islam et al. <sup>45</sup>	This study is a review of the latest publications on the modulatory effects of natural antiviral dietary supplements, vitamins, and minerals on immunity, focusing on their potential use as adjuvant therapy alongside antiviral medicines in the management of COVID-19 disease.	The review suggests that various dietary supplements, such as black seeds, garlic, ginger, cranberry, orange, omega-3 and -6 polyunsaturated fatty acids, vitamins (e.g., A, B vitamins, C, D, E), and minerals (e.g., Cu, Fe, Mg, Mn, Na, Se, Zn), have demonstrated anti-viral effects against respiratory viruses, including coronaviruses, and could be used as adjuvant therapy alongside antiviral medicines in managing COVID-19 disease.

The most prominent methods of alternative therapy against infection caused by SARS-CoV-2 are acupuncture, reflexology, biohacking, homoeopathy, and magnetotherapy.<sup>6,9,11</sup> However, the most effective were vitamin therapy and naturopathy, introduced in the form of herbal medicine. The latter type has found the greatest use in the treatment of diseases of infectious origin.<sup>12</sup> This type of treatment is considered to be on a fine

line between pharmacotherapy ("conventional" drugs) and herbal remedies. Phytotherapy can be described as a treatment method that focuses on the use of one or more medicinal plant remedies to prevent or treat a pathological condition. It should be noted, however, that existing rational herbal medicines aim to achieve an effect within the therapeutic dose without the onset of dangerous side effects on various organs and their



systems. Using alternative treatments for SARS-CoV-2 infections can have both potential advantages and disadvantages compared to conventional treatments. Here are some of the key points to consider (Table 2).

**Table 2** - Advantages and disadvantages of alternative medicine in treating SARS-CoV-2

Advantages	Disadvantages
Holistic approach: considers overall well-being and immune system support.	Limited scientific evidence to support efficacy and safety for SARS-CoV-2.
Potential for personalized care based on individual needs.	Delay in seeking proven, evidence-based conventional treatments.
Perceived lower occurrence of side effects.	Potential interactions with conventional medications.

The use of complementary and alternative medicine (CAM) therapies for SARS-CoV-2 infections is influenced by various cultural and societal factors. These include cultural beliefs, historical practices, mistrust in conventional medicine, access to healthcare, and personal experiences. In some cultures, traditional healing practices and natural remedies hold significant value and are deeply rooted in their healthcare systems. Additionally, societal factors such as misinformation, social media influence, and the desire for quick solutions may contribute to the uptake of CAM therapies.<sup>10</sup> To address these factors in healthcare settings, it is important to promote culturally sensitive care by acknowledging and respecting diverse cultural beliefs and practices. Healthcare providers should engage in open and non-judgmental communication, actively listen to patients' perspectives, and educate them about evidence-based practices and the potential risks associated with unproven CAM therapies. Collaborative decision-making, integrating CAM therapies within a comprehensive healthcare plan, and encouraging dialogue can foster trust and improve patient-provider relationships. Furthermore, healthcare systems should invest in public health campaigns to disseminate accurate information about COVID-19 and promote critical thinking skills among the population, empowering individuals to make informed choices regarding their healthcare.

Patients and healthcare providers can collaborate to ensure the safe and effective use of alternative treatments for SARS-CoV-2 infections by fostering open and honest

communication. Patients should share their interest in alternative treatments with their healthcare providers, providing accurate and comprehensive information about the treatments they are considering. Healthcare providers, on the other hand, should listen attentively, respect patient autonomy, and engage in a shared decision-making process. Together, they can discuss the potential benefits, risks, and limitations of alternative treatments, considering the available scientific evidence and individual patient circumstances. By maintaining this collaborative approach, patients and healthcare providers can work together to make informed decisions that prioritize patient safety, promote evidence-based practices, and optimize health outcomes in the context of alternative treatments for SARS-CoV-2 infections.

Kladar et al.<sup>12</sup> name certain advantages to using modern herbal medicines. Firstly, such products can be considered as a rather valuable source of secondary-order biomolecules that are characteristic of herbs. The authors note that a wide variety of substances extracted from herbs can act as immunomodulators due to a positive reaction to natural killer cells, macrophages, lymphocytes, and cytokines.<sup>12</sup> Since COVID-19 is classified as a respiratory disease, herbal remedies used to offset the symptoms associated with this type of the disease are indeed essential. The research indicates that medicinal plants are a popular and acknowledged form of therapy in combatting COVID-19. A substantial portion of respondents employ phytotherapy, viewing it as both effective and safe due to its presumed positive impact on respiratory and immune systems. The convenience of readily preparable and accepted forms contributes to its frequent use. To maximize the benefits of phytotherapy, it is recommended to utilize high-quality products with established effectiveness and safety, preferably under medical guidance.

Among the registered medicinal plants, garlic, ginger, chamomile, and others were most often referred to. Recent scientific publication<sup>12,13</sup> describe the positive effect of garlic against the symptoms caused by SARS-CoV-2, which is considered to be the result of immune activation mediated by stimulation of macrophages, lymphocytes and natural killer cells. Furthermore, garlic has been found to modulate cytokine secretion and immunoglobulin synthesis. The research of Li et al.<sup>13</sup> describe the positive effect of *Allium sativum* in eliminating the main signs of infectious diseases associated with sensitive activation of immune responses, and

through indirect activation of a complex of macrophages, lymphocytes, and natural killer cells. In addition, it was noted how cytokine accumulation and immunoglobulin Fusion can be modulated.

Garlic has been featured regularly in other publications that focus on a series of studies on the use of herbs to prevent and treat other viral diseases. In particular, ginger (*Zingiber officinale*) has been tested in cases of COVID-19 in combination with *Echinacea*, showing that the use of remedies containing these plants dramatically reduced the severity of cough, muscle pain, and shortness of breath. Although camomile has not been subjected to similar modern clinical trials in cases of COVID-19, numerous literature data suggest that camomile can be considered as an option in the treatment of respiratory syndrome in infectious diseases.<sup>6</sup> This plant has many natural pharmacological properties known to mankind (primarily anti-inflammatory), which are potentially useful in changing the dynamics of the disease.

Li et al.<sup>13</sup> focus on the case of the successful treatment of mild SARS-CoV-2 with some honeysuckle-based extracts. The scientists note that honeysuckle can effectively mitigate clinical symptoms of COVID-19 and dramatically suppress the replication of SARS-CoV-2. According to recent findings of respective scientists,<sup>13</sup> there is also evidence that a combination of honeysuckle-based preparations with medical treatment can improve diagnostic performance in computed tomography (CT) of the lungs, as well as laboratory tests, with an increase in the number of white blood cells and a decrease in C-reactive protein. Such an effect is explained by the characteristics of honeysuckle's influence on the vulnerable function of the immune system and a combination of protective inciting factors. The efficacy of honeysuckle preparations in the treatment of pulmonary infections is more likely to include several immunopathological processes, such as changes in certain laboratory parameters, including lymphocytopenia, and increased levels of cytokines, which are considered in immunology to be important factors in the progression of the disease and the risk of death in coronavirus infection.

This research highlights immune cell infiltration differences in mild COVID-19 cases, indicating potential targets for honeysuckle treatment.<sup>13</sup> Reduced NK cells and hematopoietic stem cells were observed, aligning with clinical characteristics. Two immunomodulatory genes, *RELA* and *MAP3K7*, were underexpressed and associated with NK cells and HSC. These genes could

potentially serve as markers for honeysuckle treatment, aiming to mitigate symptoms by modulating immune responses. The study suggests that honeysuckle could enhance NK cell and HSC infiltration, tempering the cytokine storm and curtailing disease progression. While the research demonstrates honeysuckle's potential in mild COVID-19, further *in vivo* and *in vitro* validation is needed to explore individual components and mechanisms thoroughly. Nonetheless, this approach offers insights into COVID-19 treatment using honeysuckle, emphasizing early intervention to prevent cytokine storms and severe outcomes.

Recent studies by contemporary researchers have demonstrated<sup>13,14</sup> that a significant proportion of activated myeloid dendritic cells and most uncontrolled T cells (Tregs) increase dramatically, and the infiltration process is rather high; the same applies to such indicators as hematopoietic stem cells, a sudden sharp decrease in the proportion of monocytes and their rather high infiltration capacity. In general, the expression of CD8 T cells, myeloid dendritic cells, and Tregs was significantly increased in mild COVID-19 symptoms. However, these cells have a high ability to inhibit the development of hematopoietic stem cells. As the infectious disease progresses, the number of NK cells rapidly decreases. This study emphasizes the importance of maintaining established methodological standards for clinical studies and SRs, even during the pandemic, to offer reliable evidence to decision-makers, clinicians, and patients. While this overview adhered to strict methodological criteria and comprehensive search methods, it underscores the need for high-quality evidence in evaluating the use of herbal medicine for COVID-19 management.

When considering cases of mild coronavirus infection, some immunomodulatory genes with a severe lack of expression, such as *RELA* and *MAP3K7*, are important in the pathogenesis. *RELA* as a key subunit of NF-Kappa-B is involved in the regulation of the stability of active T cells in the immune system. The role of the enzyme mitogen-activated protein kinase 7 (*MAP3K7*), which is responsible for encoding the transforming growth factor  $\beta$ -activated kinase 1 (*TAK1*), is significant. When the SARS-CoV-2 virus infects the body, the innate immune system is the first to respond to the detection of viral infection.<sup>15,16</sup>

Following the characterisation of the immune processes of viral infections, it is worth noting that at

this point, the number of immune NK cells decreases dramatically, and rapid synthesis of proinflammatory cytokines occurs to suppress viral replication. However, a significant release of cytokines leads to excessive inflammation, causing cytokine storms that can result in formidable serious complications of the disease. Furthermore, hematopoietic stem cells (HSCs) can divide into other immune cells and thus also provide immune antiviral function.

Some publications report that the leaves of the olive tree 15 are quite rich in phenolic resins, primarily compounds such as hydroxytyrosol, verbascoside, oleuropein, apigenin-7-O-glucoside and luteolin-7-O-glucoside. This plant is known for its compounds such as triterpenoids and ursolic acid-like oleanolic acids, which are referred to in many studies as the main metabolites involved in the fight against the SARS-CoV-2 virus. The research underscores the complexity of the actions of fat-soluble and water-soluble vitamins, emphasizing their collective impact rather than individual effects, and suggests that the immune system's response to these vitamins is intricate and not easily predictable. Focusing on vitamins A, D, E, and C, the research proposes their potential use for restoring immune system function in aged individuals at risk of infection-related mortality and for treating patients with SARS-CoV-2-mediated acute infection.<sup>15</sup>

Moreover, olive leaf-based extracts are known for their anti-inflammatory, analgesic, antipyretic, immunomodulatory, and antithrombotic properties, which have a significant effect on the cytokine storm phenomenon and also play a role in the prevention of cytomegalovirus infection.<sup>16</sup> The antiviral effect of *Ginkgo biloba*<sup>17</sup> is mediated by various mechanisms, including blocking the 3-chymotrypsin-like protease of SARS-CoV-2, which provides trans-variant efficacy. However, the *Ginkgo biloba* plant has an impressive potential to prevent the development of many pulmonary inflammatory diseases by reducing the activity of the neutrophil elastase enzyme, and releasing pro-inflammatory cytokines that suppress anti-inflammatory phenomena, platelet aggregation, and thrombosis. That is precisely why it is believed that *Ginkgo biloba* can offset acute lung damage and acute respiratory syndrome, which is characteristic of COVID-19. The research presents controlled experimental evidence that local tissue biomechanical properties influence the uptake of SARS-CoV-2 viral particles by cells. Successful infections appear

to depend on the combination of appropriate tissue elasticity, where softer tissues enhance infection rates, particularly for the D614G variant, along with sufficient ACE-2 expression.<sup>17</sup>

Studies by other researchers provide data on the treatment with such plants as *Thymus serpyllum*, small-leaved linden (*Tilia cordata* Mill), chamomile (*Matricaria chamomilla*), raspberry, coltsfoot (*Tussilago farfara*), Fennel (*Foeniculum vulgare*), Liquorice (*Glycyrrhiza glabra*), sage (*Salvia officinalis*), peppermint (*Mentha piperita*), *Calendula officinalis*, garlic (*Allium sativum*), nettle (*Urtica dioica*), nasturtium (*Tropaeolum*), etc.<sup>18</sup> Subsequently, all of these plants were used to reduce complex inflammatory diseases to a mild form and to alleviate symptoms such as dry cough and shortness of breath.

The use of herbs for cough relief is mainly aimed at eliminating secretions from the lungs and thus facilitating expectoration. An analysis of scientific data indicates that such remedies are mostly produced in the form of colourful lozenges, similar to teas (sauces are added to boiling water), decoctions (boiled), infusions (raw herbs are added to alcohol and left to infuse), etc.<sup>18</sup> For example, horsetail herbal tea can be used to relieve coughs. These herbs can be used for other diseases that occur following SARS-CoV-2 infection, such as urinary tract infections and even superficial wounds. Mint tea and mint infusions are widely used for cough relief and inhalation in case of cough and nasal congestion. Based on current recommendations,<sup>18</sup> mint leaves can be successfully used to treat infectious and inflammatory diseases of the digestive system (e.g., diseases accompanied by dyspepsia, and bloating).

*Hypericum* is commonly used for sore throats and coughs. However, scientific sources indicate that *Hypericum* is often used for anxiety conditions resulting from viral illnesses.<sup>18</sup> Also, the *Hypericum* plant proves useful for poisonings, but most often for infectious diseases that lead to gastrointestinal dysfunction. Concentrates of some substances of the coltsfoot plant have a great hepatotoxic effect. For a long time, the use of coltsfoot herbs has been restricted, especially those containing the substance pyrrolizidine, and subsequent studies have been recommended due to a lack of data on human toxicity. As for COVID-19, it usually manifests itself in the form of respiratory symptoms, such as severe pneumonia and acute respiratory distress syndrome in severe cases; it can also lead to many extrapulmonary

complications. The pathogenesis of extrapulmonary complaints in COVID-19 cases is likely multifactorial and includes direct products of SARS-CoV-2 as well as circulatory mechanisms associated with the host's inflammatory response.

Despite the fact that SARS-CoV-2 mainly causes respiratory diseases, new evidence has been found that SARS-CoV-2 can also affect the central nervous system (CNS) and even the peripheral nervous system (PNS), causing a variety of neurological conditions such as encephalitis, encephalopathy, Guillain-Barré, meningitis, and muscle diseases.<sup>18</sup> According to recent scientific data, coronaviruses can reach the CNS, causing neurovirulence.<sup>18</sup> Nevertheless, the exact pathway and mechanisms by which coronaviruses enter the CNS are not fully understood at this point.

Generally, viral infections start in the accessory apices, spread to additional nerve cells, and eventually reach the central nervous system. Al-Kuraishy et al.<sup>19</sup> report that in vivo trials, *Ginkgo biloba* extract (EGb) reduced fear and anxiety, improved sleep, and eliminated gastrointestinal conditions caused by stress. Allegedly, the essential oil of *Ginkgo biloba* leaves revealed the depressant effect of mint leaves on the central nervous system in preparations corresponding to both types of raw materials. Passionflower extract is also included in clinical trials for cases with anxiety symptoms.<sup>19</sup> The anxiolytic effect of passionflower has been extensively studied, but it is still unknown which compounds in the extract are responsible for it. The research reveals that EGb possesses strong anti-inflammatory, antioxidant, and antiviral properties, including anti-SARS-CoV-2 effects by influencing proinflammatory cytokines, endothelial dysfunction-related thrombotic issues, and the progression of lung-related complications in COVID-19 patients.<sup>19</sup> Structural and biological evaluations suggest its effectiveness against various SARS-CoV-2 variants. EGb holds promise as a potential therapy for managing COVID-19. However, further assessment is needed to balance its benefits and risks, and clinical trials are required to establish its efficacy. The utilization of GB-based nanomedicine is also considered as a potential avenue for enhanced therapeutic effects.<sup>19</sup>

## Discussion

Recent study on the characteristics of *Rhodiola rosea* or *Rhodiola officinalis* roots have shown a

significant increase in the concentration of hormones such as norepinephrine, serotonin, dopamine, and acetylcholine, which are involved in the activity of the central nervous system (CNS), as well as stimulation of adrenocorticotrophic hormone accumulation.<sup>19</sup> *Rhodiola rosea* extracts significantly increase the distribution and role of liver glycogen, and heat shock protein expression.<sup>19</sup>

Vitamin supplements play an extremely important role in the prevention and treatment of SARS-Cov-2 infection, especially C and B vitamins.<sup>19</sup> Vitamin C, the most commonly cited vitamin, plays an important role in the human body, particularly when it comes to the significance of vitamins in the functioning of the immune system. Previously published studies report only on its use for the treatment of COVID-19, and there is no data on the prevention of symptoms.<sup>17,19</sup> It is impossible to draw a universally applicable conclusion, although a therapeutic effect has been observed in cases with severe clinical manifestations of coronavirus infection. Many antiviral drugs derived from vitamin C can be considered among the most effective in treating people with COVID-19. Vitamin C successfully suppresses the factors favourable for infections and stimulates the formation of protective interferon. Vitamin C significantly enhances the antiviral effect of lung epithelial cells.<sup>20</sup>

Nutritional supplements and mixtures with vitamin C help reduce the risk and level of oxidative stress and, therefore, prevent damage to the endothelium of internal vessels.<sup>21,22</sup> This suggests that vitamin C may protect against cytokine attack during SARS-CoV-2 infections. Tumour necrosis factor (TNF- $\alpha$ ) and other proinflammatory cytokines are reduced by vitamin C, while anti-inflammatory cytokines increase interleukin 10 (IL-10). Vitamin C treatment dramatically reduces interleukin IL-6 levels and inhibits endothelin-1 (ET-1), causing IL-6 release in the endothelium in vivo.<sup>23</sup>

Vitamin C can achieve extremely high efficacy in the treatment of severe pneumonia, because this compound is also closely related to the cascade of reactions. Ascorbic acid plays a crucial role in the functioning of innate immune cells, including their proliferation and isolation. It is also a vital antioxidant that can neutralise reactive oxygen species and regulate the expression of pro-inflammatory modulators and other harmful factors.<sup>24</sup> Severe pneumonia is preceded by so-called crash reactions in the body, which disrupt gas exchange and contribute to all the conditions for sepsis and organ dysfunction. Vitamin C reduces the level of oxidative

stress and pro-inflammatory intercessors in cases of severe community-acquired pneumonia.

As for vitamin D, the trend for this fat-soluble vitamin has increased dramatically since the outbreak of the pandemic. Because vitamin D deficiency is associated with increased prevalence or maladaptation of viral states, vitamin D supplementation can significantly reduce the risk of infection. Vitamin D has several mechanisms by which it can reduce the risk of microbial infection and mortality.<sup>24</sup> These mechanisms can be divided into physical defence, natural cellular disorder, and adaptive immune disorder. As it is known from the latest sources,<sup>24</sup> the vitamin D compound protects the airways by maintaining strong ligaments, destroying infections coated with cathelicidin and defensin, and reducing the production of pro-inflammatory cytokines by innate immune properties, thus potentially slowing down the rate of virus replication and eliminating several symptoms. The immunomodulatory component of vitamin D can mitigate innate disorders at the molecular level by accumulating antiviral peptides that increase mucosal resistance by affecting both TNF- $\alpha$  and interferon- $\gamma$ . The innate immune system synthesises both proinflammatory and anti-inflammatory cytokines in response to pathological viral and bacterial agents, as observed in cases of COVID-19. Vitamin D may also be beneficial in creating the necessary conditions for the production of proinflammatory Th1 cytokines such as TNF- $\alpha$  and interferon- $\gamma$ .<sup>25</sup> It also reduces the production of proinflammatory cytokines and stimulates macrophages to induce anti-inflammatory cytokines, etc.

The severe acute respiratory form (SARS-CoV-2) largely utilises immune complexes in the infection process. Accordingly, the release of numerous proinflammatory cytokines, such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , which are associated with severe vascular hyperpermeability, severe lung damage, multiple organ failure and reduced responsiveness to COVID-19, followed by a hyperpermeability reaction, which can develop into the pathological process of an acute respiratory syndrome.

According to scientific data,<sup>26</sup> deficiency of vitamin D<sup>26,27</sup> and lack of activation of the vitamin D receptor (VDR) can significantly complicate respiratory symptoms associated with SARS-CoV-2, as it causes an early response in specific stellate cells (astrocytes) of the lungs. However, numerous studies support the hypothesis that vitamin D is able to reparate epithelial layers and damaged organs, and the administration of this vitamin

in relation to pathologies that cause inflammation, such as fibrosis, also demonstrates an antifibrotic effect.<sup>28</sup> Despite the abundance of data supporting the beneficial effects of vitamin D on SARS-CoV-2 infections, such evidence is still limited, heterogeneous, and highly controversial, and the involvement of this compound in the regulation of both internal and adaptive immune systems easily suggests that the therapeutic properties of this vitamin have a legitimate basis.<sup>29</sup> This issue raised by Muscogiuri et al.<sup>29</sup> was preliminary developed on the basis of specific native expression of surface pathogen recognition receptors and their TLR-like proteins to identify the hostile agent and further enable the prevention and treatment of infectious disease. Compound 25(OH)2D, compared to other substances, enhances the defence mechanism by converting harmful substances like cathelicidin, which affect the destruction and breakdown of the virus and simultaneously act through several mechanisms.<sup>29</sup>

Zinc is arguably the most commonly referred to macronutrient in this study as an alternative health supplement and is an important micronutrient that prevents infection and the re-propagation of viruses or bacteria. An analysis of scientific clinical data revealed that the use of this compound in an epidemic or pandemic can reduce the frequency and duration of most viral diseases.<sup>30</sup> Thymulin is involved in the chemical process of synthesis of immune natural T cells, the development and action of natural killer cells (NK). Moreover, an important role of zinc is its participation in the confluence of IFN- $\gamma$ , IL-2, and IL-12 products when stimulated by specific macrophages. IL-12 induces the activation of cytotoxic T cells and NK cells. And the latter, in turn, plays an important role in the destruction of pathogens. Zinc deficiency leads to dysregulation of IL-10 (an anti-inflammatory cytokine), which affects the Th1 response and macrophage function.<sup>31</sup> Zinc is one of the most abundant macronutrients in the living body and plays a valuable role in modulating the immune system, so these reactions are similar to CD8 T-cell responses and activation of so-called specific adjuvant T cells. Its involvement in the synthesis of IFN- $\gamma$ , IL-2, IL-12, and activation of T-cytotoxic cells and NK cells may be associated with the destruction of pathogens. Zinc deficiency affects the conformation of IL-10, which influences the Th1 response and macrophage function.<sup>32</sup>

Rather ambiguous data indicate that zinc supplementation may be associated with the development

and functional stress of immune major cells of the innate immune response, such as neutrophils and NK cells.<sup>33</sup> Nevertheless, zinc deficiency can be fatal for the synthesis of cytokines and for the organism as a whole.<sup>34,35</sup>

The above-mentioned macronutrient is capable of modulating a large number of specific substances in the human body, as well as antiviral and antibacterial activity and regulates the body's reactivity response. An *in vitro* study shows that zinc has an antiviral effect by inhibiting RNA polymerase, which reacts during the COVID-19 reaction cascade.<sup>36</sup> This can enhance the therapeutic efficacy of chloroquine, which is a zinc ionophore. It can also inhibit the activity of the COVID-19 ACE2 receptor. Significant improvement of the antiviral effect of zinc may be accompanied by an increase in the formation of interferon and enhancement of its antiviral effect. Zinc can exert anti-inflammatory effects by inhibiting NF- $\kappa$ B signalling and modulating non-controlling functions of immune T cells, which can limit the COVID-19 cytokine storm.<sup>37</sup>

Selenium (selenoprotein proteins and selenium-containing foods and substances) may exhibit its anti-COVID-19 effect precisely by sharply reducing the expression of the membrane receptor ACE-2 (prevents SARS-CoV-2 from entering the cell); and another mechanism is a sharp decline in the synthesis of pro-inflammatory substances (these are the so-called compounds that slow down the cytokine storm, oxidative stress, ARVI, etc.) and inhibition of 3CLPro (the main protease enzyme) of SARS-CoV-2. An acceptable amount or dosage of selenium in the human body allows for avoiding a formidable cytokine storm due to its anti-inflammatory and antioxidant properties, stops SARS-CoV-2 from entering a living cell by suppressing the expression of ACE-2 receptors, and inhibits the SARS-CoV-2 enzyme.<sup>38</sup> Selenium is essential for the functioning of special cytotoxic immune CD8 T and NK cells. Selenium significantly enhances the lytic activity of already activated NK cells. This macronutrient enhances the proliferation process, as well as the expansion and lytic activity of some cells by lymphokines by aggregating and increasing the expression of IL-2 surface receptors on these cell membranes. Significant clinical benefits of selenium-containing nutraceuticals have been demonstrated in HIV-1 hepatitis B-related liver cancer.<sup>39</sup>

Recent findings suggest that there is no significant effect of a favourable intake of vitamins B1, B2, B3, B9, and B-complex on COVID-19.<sup>40</sup> However, a significantly increased intake of vitamin B5 in some cases can

reduce the risk of COVID-19 infection, and accordingly, moderate intake of vitamin B12 offers perhaps the most beneficial protective effect against COVID-19.<sup>41</sup> More recent studies have estimated that traditional Chinese medicine (TCM) is considered one of the alternative methods that can correct imbalances in the intestinal environment, stimulate the growth of beneficial bacteria, and inhibit the overgrowth of harmful bacteria.<sup>42-44</sup> The TCM has been actively engaged in the entire process of prevention, treatment and recovery throughout the epidemic, supplemented and combined with Western medicines, making important contributions and playing a unique role in the comprehensive control of COVID-19.<sup>45</sup>

Notably, the timely use of traditional medicine can dramatically reduce the aggressive response, minimise a vulnerable function, improve the impact of immersive pneumonia, and reduce mortality in severe cases of COVID-19.<sup>16</sup> The integration of alternative TCM can help relieve fever, cough, expectoration, fatigue, chest tightness, and anorexia; shorten the duration of fever and cough; shorten hospital stay; reduce the severity of symptoms; help resolve pneumonia and nucleic acid metamorphosis; and improve the overall response and cure rate.

As for other alternative therapies, such as acupuncture, reflexology, biohacking, and magnetic therapy, no reliable sources have been found to indicate their effectiveness in combating SARS-CoV-2. Presumably, the methods described above are only an additional approach to the treatment or prevention of certain psychotic conditions, such as anxiety that occurs in the context of SARS-CoV-2 infection. Moreover, such methods are rather neurogenic in origin and can remedy some symptoms arising from the nervous or musculoskeletal system.

## Conclusion

In summary, alternative therapies for SARS-CoV-2 infections encompass a wide array of approaches, including acupuncture, reflexology, biohacking, homeopathy, magnetotherapy, and vitamin therapy, with naturopathy and herbal medicine emerging as particularly effective methods. The latter utilizes medicinal plants with immunomodulatory and antiviral properties, addressing various aspects of the disease. However, the utilization of alternative treatments raises both potential advantages and disadvantages when compared to

conventional approaches. Cultural and societal factors play a significant role in the adoption of CAM therapies, making culturally sensitive care and open patient-provider communication crucial. Collaborative decision-making between patients and healthcare providers is essential to ensure the safe and effective integration of alternative treatments, while maintaining evidence-based practices.

The research underscores the significance of herbal medicines in alleviating COVID-19 symptoms, focusing on substances like garlic, ginger, chamomile, and honeysuckle. These herbs exhibit immunomodulatory effects, influencing various immune cells and cytokines, thus potentially mitigating the cytokine storm and supporting the immune response. Moreover, olive leaf extracts, Ginkgo biloba, and EGb present antiviral and anti-inflammatory properties, contributing to disease management. The understanding of immunomodulatory genes like RELA and MAP3K7 sheds light on potential targets for honeysuckle treatment, emphasizing the importance of early intervention to curb disease progression. However, further validation through in vivo and in vitro studies is required to comprehensively explore these approaches.

Overall, the exploration of alternative treatments for SARS-CoV-2 infections presents a complex landscape that combines traditional practices with contemporary scientific findings. Integrating culturally sensitive care, evidence-based practices, and open patient-provider communication is paramount in ensuring the safe and effective utilization of alternative therapies within the context of the pandemic.

### Authors' contributions

Each author has participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript and that each author has approved the manuscript as submitted. All authors agree to be accountable for all aspects of the work.

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