Russian Journal of Infection and Immunity = Infektsiya i immunitet
2023, vol. 13, no. 4, pp. 709–722

Инфекция и иммунитет
2023, Т. 13, № 4, с. 709–722

# PROBIOTICS IN PREVENTION AND TREATMENT OF COVID-19: A SYSTEMATIC REVIEW OF CURRENT EVIDENCE

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**Abstract.** *Introduction.* Clinical evidence suggests that certain probiotics may help treat and prevent viral infections. To date, the effectiveness of probiotics in the alleviation of COVID-19 has not been established. The aim of this systematic review was to assess the role of probiotics in the prevention and treatment of COVID-19. *Materials and methods.* An extensive search of four electronic databases was performed which included Embase, Scopus, Web of Science, and PubMed from November 2019 to June 2022. After reviewing the references list of related articles additional studies were identified. A multiple combination of keywords validated by MESH were used to search the databases. Study selection was performed according to an inclusion and exclusion criteria. *Results.* Twenty-three articles met the study inclusion criteria. Six articles were conducted *in vitro* while the remaining studies were conducted in the human population (*in vivo*). The type of probiotic was defined in eighteen studies. There were two studies that used supplements (vitamins, herbals, minerals, etc.) in addition to probiotics. The largest sample size was 445 850 participants which were from a study that used an application-based survey. The majority of studies found that probiotics had a positive effect on the COVID-19 disease. The benefits included early remission of COVID-19 symptoms and a shorter duration of sickness (10 studies), lower mortality rates (3 studies), and decreased hospitalization and length of stay (3 studies). Six *in vitro* studies found that probiotics were beneficial against SARS-CoV-2 through antiviral effects. There were only two studies that found probiotics to be ineffective or caused negative effects when consumed in COVID-19 patients. *Conclusion.* Available evidence supports the antiviral role of probiotics on prevention and treatment of COVID-19. The antiviral potential of *Lactobacillus paracasei* metabolite PlnE and PlnF against SARS-CoV-2 may explain the effectiveness of probiotics on COVID-19.

***Key words:*** *COVID-19, SARS-CoV-2, 2019-nCoV, probiotics, treatment, prevention.*

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**Для цитирования:**
СейедАлинаги С., Шахиди Р., Афзалян А., Паранджху П., Горбанзадех К., Мождеганлу Х., Рази А., Мождеганлу П., Дашти М., Гасемзаде А., Парихани С.Н., Пашай А., Карими А., Ахмади С., Мехраин Э., Хакетт Д. Пробиотики в профилактике и лечении COVID-19: систематический обзор современных данных // Инфекция и иммунитет. 2023. Т. 13, № 4. С. 709–722. doi: 10.15789/2220-7619-PIP-2118

**Citation:**
SeyedAlinaghi S., Shahidi R., Afzalian A., Paranjkhoo P., Ghorbanzadeh K., Mojdeganlou H., Razi A., Mojdeganlou P., Dashti M., Ghasemzadeh A., Parikhani S.N., Pashaei A., Karimi A., Ahmadi S., Mehraeen E., Hackett D. Probiotics in prevention and treatment of COVID-19: a systematic review of current evidence // Russian Journal of Infection and Immunity = Infektsiya i immunitet, 2023, vol. 13, no. 4, pp. 709–722. doi: 10.15789/2220-7619-PIP-2118



**DOI:** http://dx.doi.org/10.15789/2220-7619-PIP-2118

# ПРОБИОТИКИ В ПРОФИЛАКТИКЕ И ЛЕЧЕНИИ COVID-19: СИСТЕМАТИЧЕСКИЙ ОБЗОР СОВРЕМЕННЫХ ДАННЫХ

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**Резюме.** *Введение.* Клинические данные свидетельствуют о том, что некоторые пробиотики могут быть полезны в лечении и профилактике вирусных инфекций. Однако эффективность пробиотиков при COVID-19 на сегодняшний день не установлена. Цель настоящего систематического обзора заключалась в оценке роли пробиотиков в профилактике и лечении COVID-19. *Материалы и методы.* Был проведен расширенный поиск информации по обозначенному выше вопросу в четырех электронных базах данных, включая Embase, Scopus, Web of Science и PubMed, во временном интервале с ноября 2019 г. по июнь 2022 г. После изучения списка соответствующих статей были определены дополнительные поисковые ограничения. Для поиска в базах данных использовалось несколько комбинаций ключевых слов, проверенных MESH. Отбор исследований осуществлялся в соответствии с критериями включения и исключения. *Результаты.* Двадцать три статьи соответствовали критериям включения в исследование. В шести статьях была информация об исследованиях, проведенных *in vitro*, в остальных — об исследованиях, проведенных у людей *(in vivo)*. Тип пробиотика был указан в восемнадцати исследованиях. В двух исследованиях в дополнение к пробиотикам использовались пищевые добавки (витамины, травы, минералы и т. д.). Самый большой размер выборки составил 445 850 участников, опрос которых проводился в мобильном приложении COVID Symptom Study. Большинство исследований показало, что пробиотики оказывают положительное влияние на течение COVID-19, что проявляется в начале ремиссии симптомов COVID-19 на ранних сроках заболевания и в более короткой продолжительности болезни (по данным 10 исследований), в более низких показателях смертности (3 исследования), а также в снижении числа госпитализаций и продолжительности пребывания в стационаре (3 исследования). Шесть исследований *in vitro* показали, что пробиотики были эффективны в отношении SARS-CoV-2 благодаря противовирусному действию. Только два исследования показали, что пробиотики при COVID-19 неэффективны или их применение приводят к негативным последствиям. *Выводы.* Имеющиеся данные подтверждают роль пробиотиков в профилактике и лечении COVID-19. Эффективность пробиотиков при COVID-19 может быть объяснена наличием противовирусного потенциала бактериоцинов PlnE и PlnF *Lactobacillus paracasei* в отношении SARS-CoV-2.

***Ключевые слова:*** *COVID-19, SARS-CoV-2, 2019-nCoV, пробиотики, лечение, профилактика.*

## Introduction

The coronavirus disease 2019 (COVID-19) has rapidly spread from China around the world and is considered a global pandemic. As of early December 2021, 263 000 000 people across five continents have been infected by COVID-19 [15, 54]. This disease has emerged as a multifaceted, multisystem and multi-organ disorder ranging from nonspecific flu-like symptoms, to pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure and death [5, 36].

Supplementing with non-pharmacological substances such as probiotics and nutraceuticals has been suggested as a potential therapeutic option for COVID-19, due to evidence of an interference effect on the SARS-CoV-2 pathway [25]. Specifically, probiotics with anti-inflammatory or immunomodulatory properties may be the most effective for prevention or alleviation of COVID-19 symptoms [8]. In early February 2020, China's National Health Commission and National Administration (version 5) recommended the use of probiotics and gut microecological modulators in COVID-19 patients to maintain the balance of intestinal microecology [67].

Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit to the host [1]. Probiotics exert their beneficial effects through various mechanisms including manipulation and restoration of gut microbiota, enhancement of intestinal barrier function, and competition with pathogens for adhesion to gut epithelium and nutrition, and suppression of opportunistic pathogens. Other potential mechanisms explaining how probiotics may promote beneficial effects include the production of antimicrobial substances, decrease in translocation of opportunistic organisms, activation of mucosal immunity, and modulation of the innate and adaptive immune response [66].

Although the rationale for using probiotics to treat COVID-19 comes from indirect evidence, it is mechanistically plausible that probiotics may help in the prevention of and/or alleviation of COVID-19 related symptoms and complications. Moreover, probiotics are readily available, easy to administer (oral administration), relatively safe and economical compared with antiviral drugs, immunomodulators or other strategies tested in COVID-19 [4]. There is clinical evidence showing that certain probiotics may help treat and prevent viral infections [67]. However, the role of probiotics in alleviation of the novel COVID-19 has not been established. The aim of this systematic review was to assess the role of probiotics in the prevention and treatment of COVID-19.

## Materials and methods

*Study objective and search strategy.* An extensive search of four electronic databases was performed which included Embase, Scopus, Web of Science, and PubMed from November 2019 to June 2022. After reviewing the references list of related articles additional studies were identified. A multiple combination of keywords validated by MESH was used as the search strategy. Only English and Persian studies were included in the search. The search strategy is presented in Table 1. This systematic review was conducted according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [41].

*Inclusion/exclusion criteria.* Articles were eligible for inclusion if they met the following criteria: (1) randomized controlled trials, cross sectional, case series, case reports, and cohort studies; (2) examined the effect of a probiotic on outcomes related to immunity, immunological responses, or signs/symptoms/severity of COVID-19; (3) involved adult humans that were 18 years old or older; (4) experiment was conducted either *in vivo* or *in vitro*, and (5) published in English and Persian. Articles were excluded if they were non-original, review papers, commentaries, or editorials.

*Screening and selection.* A two-step method was performed to improve the study selection process. After removing duplicate articles, step-one was performed which involved screening of titles and abstracts of retrieved. For step-two the full-text of articles that were potentially eligible were assessed by two reviewers to confirm eligibility. Articles were compiled in an Endnote X9© (Thomson Reuters) file.

*Data extraction.* A standardised template was used by the researchers to complete data extraction. The information extracted included the first authors' name, type of study, date of study, study population, characteristics of participants, probiotic type, doses of probiotic, comparator group, effects of probiotic on cytokines and serum ingredients, and other relevant outcomes. Two independent researchers extracted and entered the information into the template.

## Results

The database search yielded 690 potential studies (after 649 duplicates were removed), and following the screening, a total of 23 studies met the eligibility criteria (Fig.). The description of the studies included is detailed in Table 2. Six articles were conducted *in vitro* while the remaining studies were conducted in the human population (*in vivo*). The type of probiotic was defined in eighteen studies. There were two studies that used supplements (vitamins, herbals, minerals, etc.) in addition to probiotics. The largest sample size was 445 850 participants which were from a study that used an application-based survey [34]. The smallest sample size of the included studies was 30 participants [59].

**Table 1. Search strategy keywords**

| Concepts | Search strategy |
|---|---|
| **Disease** | COVID-19 OR SARS-CoV-2 OR COVID-19 OR SARS-CoV-2 OR coronavirus disease 2019 OR Severe acute respiratory syndrome coronavirus 2 OR SARS CoV 2 OR 2019 Novel Coronavirus OR 2019-nCoV OR 2019 nCoV OR Coronavirus Disease-19 OR Coronavirus Disease 19 OR SARS Coronavirus 2 OR Wuhan Seafood Market Pneumonia Virus OR Wuhan Coronavirus OR Coronavirus disease 2 OR Coronavirus disease 2019 OR coronavirus infection 2019 OR COVID OR nCoV 2019 OR new coronavirus pneumonia OR Novel coronavirus OR SARSCoV2 OR severe acute respiratory syndrome 2 OR severe acute respiratory syndrome coronavirus 2019 infection OR severe acute respiratory syndrome CoV-2 infection OR 2019 new coronavirus OR coronavirus SARS-2 OR HCoV-19 OR Human coronavirus 2019 OR nCoV-2019 OR novel 2019 coronavirus OR SARS-2 (virus) OR SARS-2-CoV OR SARS-related coronavirus 2 OR SARS2 (virus) OR Severe acute respiratory coronavirus 2 OR Severe acute respiratory syndrome 2 OR Severe acute respiratory syndrome corona virus 2 OR Severe acute respiratory syndrome coronavirus 2019 OR Severe acute respiratory syndrome coronoavirus 2 OR Severe acute respiratory syndrome coronvirus 2 OR Severe acute respiratory syndrome CoV-2 virus OR Severe acute respiratory syndrome related coronavirus 2 OR Severe acute respiratory syndrome virus 2 |
| **Variable** | Probiotics OR Prebiotics OR Probiotic OR Prebiotic OR probiotic agent OR prebiotic agent |

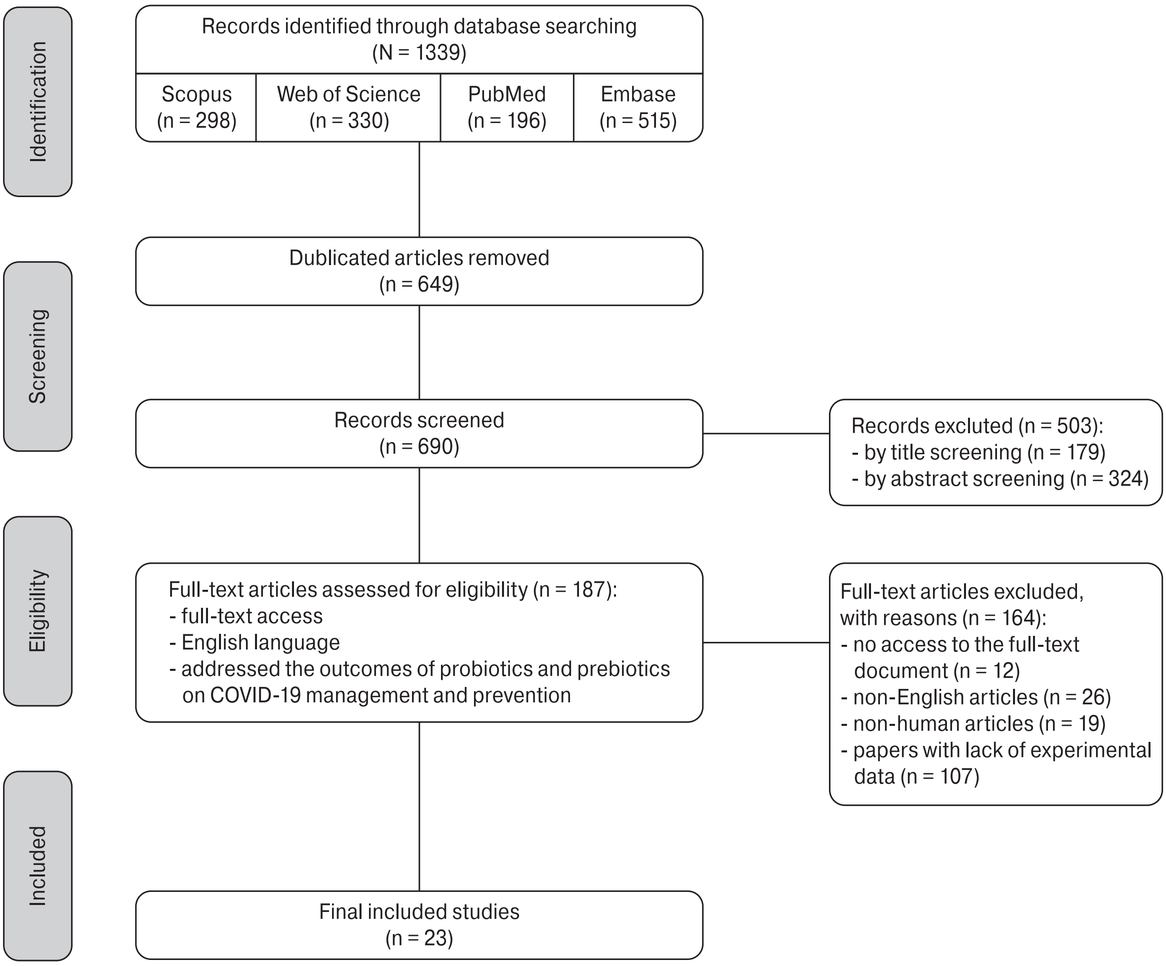


**Figure. PRISMA flow diagram of study retrieval process**

Most studies (n = 20) confirmed that probiotics were effective in COVID-19 illness. Ten studies found that consumption of probiotics led to early remission of COVID-19 symptoms and a shorter duration of sickness. Meskina et al. stated that probiotics helped patients' COVID-19 symptoms resolve faster [38]. In three studies, lower mortality was seen in patients who consumed probiotics.

Three studies reported that patients taking probiotics had decreased hospitalization and length of stay [9, 38, 67]. Two studies claimed that probiotic consumption is linked to earlier lung CT scan resolution in patients [31, 38]. According to Bozkurt et al., probiotic use is associated with lower mortality and earlier lung CT scan resolution [14] and other studies found probiotics helpful to resolve diarrhea.

Wang et al. reported that for COVID-19 patients that began taking probiotics, their COVID-19 test results became negative faster and diarrhea resolved sooner compared to patients that did not consume probiotics [62]. Six *in vitro* studies found some probiotics to be beneficial against SARS-CoV-2 through antiviral effects, preventing its replication or modulating ACE2 and inflammatory cytokines. Rather et al., reported that *L. plantarum* had a meaningfully beneficial effect on preventing SARS-CoV-2 replication [47]. Potentially this ability may be caused by plantarcin E and F. There were two studies that discussed COVID-19 reinfection. Li et al. claimed that probiotics can decrease secondary infection through immunity moderation [32]. The other study by Veterini et al. reported that two individuals in a non-probiotic group experienced reinfection, while no reinfection was seen in a group that consumed probiotics [59].

In contrast to the positive findings reported on consumption of probiotics, there were some studies which demonstrated that probiotics were ineffective or even had negative effects on the course of COVID-19 infection. According to Hegazy et al., probiotic yoghurt consumption in the 12 months preceding COVID-19 infection was linked to more severe disease [24]. Ivashkin et al. reported that the studied probiotic had no meaningful effect on the COVID-19 severity [21, 32]. Finally, Li et al. claimed that consumption of probiotics did not decrease IL-6 and length of hospitalization was higher in probiotic group [26].

**Table 2. Description of the findings reported in eligible studies**

| ID | First author | Country | Year of publication | Type of study | No. of participants | Participants characteristics | Probiotics | Dose | Comparators | Effects of probiotics | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Barber M.S. [6] | USA | 2021 | Retrospective (chart review) | 30, mean age: 45.47±22.13 | Mild, Moderate | – | – | – | – | Patients who consumed probiotics, vitamins, and minerals experienced remission of mild and moderate symptoms |
| **2** | Bozkurt H. [14] | Turkey | 2021 | Retrospective | 44, Adults ≥ 18 years | Moderate, Severe | *Bifidobacterium* | 1 trillion CFU in 250 ml water (3 divided doses per day) | Anti-interleukin-1, Anti-interleukin-6, Antibiotics, Immune plasma | IL-6↓ | Probiotic consumption linked to earlier Lung CTscan resolution in patients. Length of hospitalization↓ Mortality↓ |
| **3** | D\`Ettorre G. [16] | Italy | 2020 | Cohort | 70, 59±14.4 and 60.5±14.2 | Severe | *L. plantarum* DSM 32244, *L. acidophilus* DSM32241, *L. brevis* DSM 27961, *L. paracasei* DSM32243, *B. lactis* DSM 32246 and DSM 32247, *L. helveticus* DSM 32242, *Streptococcus thermoophilus* DSM 32345 | 2400 billion bacteria daily (3 divided doses per day) | COVID-19 medications was given to both probiotic and non-probiotic groups | – | Bacterial supplement had a meaningful beneficial effect on COVID-19 infection. Early resolve of symptoms (such as diarrhea) Mortality ↓ Eight times lower respiratory deterioration |
| **4** | Ezzat A. [17] | Egypt | 2022 | *In vitro* | – | – | Levans Lev9A (*Bacillus subtilis* 9A) LevanAE (*Pseudomonas aeruginosa*) levG (*Enterococcus faecalis*) Lev13M LevH | – | – | – | In this study LevAE Lev9A and Lev13A were found to have meaningful antiviral effects on coronavirus |
| **5** | Gutierrez-Castrellon P. [21] | Mexico | 2022 | RCT | 300, 18–60 years old | Mild, Moderate | *Pediococcus acidilactici* KABP021 + *Lactiplantibacillus plantarum* KABP022, KABP023, KAPB033 | – | Placebo | Specific IgM, IgG↑ hsCRP↓ Nasopharyngeal viral load↓ D-dimer↓ | Probiotics shortened duration of COVID-19 symptoms in patients and decreased the infiltrations in chest CT scan. Probable beneficial effect of probiotic occurs through effects on the immune system |
| **6** | Gutierrez-Castrellon P. [22] | Mexico | 2022 | RCT | 70 | – | *Lactiplantibacillus plantarum* CECT7484, CECT7485, CECT30292, *Pediococcus acidilactici* CECT7483 | $2 \times 10^9$ CFU daily (30 days) | Placebo | IFNα↑ IFNβ↑ SARS-CoV2-specific IgM↑, IgG↑ | Probiotic caused higher serum level of Interferons which is linked to increased IgM and IgG and early remission of some COVID-19 symptoms |
| **7** | Hegazy M. [24] | Egypt | 2022 | Cohort | 200 Mild: mean age = 37 Moderate: mean age = 45 | Mild, Moderate | – | – | – | Serum ferritin↑ | Probiotic yoghurt consumption during 12 months before the disease linked to more severe disease. Patients with no history of probiotic yoghurt intake experienced more gastrointestinal discomfort and diarrhea |

**Table 2. Description of the findings reported in eligible studies (continued)**

| ID | First author | Country | Year of publication | Type of study | No. of participants | Participants characteristics | Probiotics | Dose | Comparators | Effects of probiotics | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **8** | Ivashkin V. [26] | Russia | 2021 | RCT | 200<br>Probiotic group: 65 (59–71)<br>Control group: 64 (54–70) | – | *Bifidobacterium longum* subsp. *infantis* PDV1911, *Bifidobacterium longum* subsp. *longum* PDV 2301, *Bifidobacterium bifidum* PDV 0903, *Lacticaseibacillus rhamnosus* PDV 1705 | – | COVID-19 medications was given to both probiotic and non-probiotic groups | – | Probiotic had no meaningful effect on COVID-19 severity<br>Helpful for relieving diarrhea in COVID-19 patients. Probiotics beneficial to prevent nosocomial diarrhea in patients consuming one antibiotic |
| **9** | Ke E. [28] | China | 2020 | – | 800 | – | – | – | – | – | Probiotics beneficial to reduce duration of illness and resolve diarrhea in COVID-19 patients |
| **10** | Leal-Martinez F. [31] | Mexico | 2022 | RCT | 80<br>Mean age (Probiotic group ): 51.5±11.4<br>Control group: 53.9±10.3 | Severe | *Saccharomyces boulardii* | 500 mg per day (6 days) | COVID-19 medications was given to both probiotic and non-probiotic groups | – | A nutritional supplement (consisting of probiotics, vitamins, minerals, amino acids...) had a meaningful beneficial effect on COVID-19 patients. Mortality↓<br>Need for ventilation↓<br>Mortality in intubated patients↓ |
| **11** | Li Q. [53] | China | 2021 | Retrospective | 311<br>60.1±12.37 | Severe | 1 *(Bifidobacterium longum + Streptococcus thermophiles + Lactobacillus bulgaricus)* tablet<br>2 *(Lactobacillus acidophilus + Bifidobacterium infantis + Bacillus cereus + Dung enterococcus)* tablet<br>3 *(Bacillus subtilis + Enterococcus faecium)* capsule | First combination: 2 g TDS<br>Second combination: 1.5 g TDS<br>Third combination: 0.5 g TDS | COVID-19 medications was given to both probiotic and non-probiotic groups | IL-6↑<br>ESR↑<br>Total T cells↑ | Probiotics did not decrease IL-6<br>Length of hospitalization was higher in probiotic group<br>Probiotics can decrease secondary infection through immunity moderation |
| **12** | Louca P. [34] | UK, USA, Sweden | 2021 | Cohort (online application survey) | 445 850<br>UK: probiotic: 49.57±14.2<br>Non-probiotic group: 46.26±14.4<br>USA: probiotic: 56.24±15.2<br>Non-probiotic: 47.8±16<br>Sweden: probiotic: 49±13<br>Non-probiotic: 46.63±12.9 | – | – | – | – | – | Women who consumed probiotics, Omega-3 or Vitamin D were less infected with corona disease<br>This correlation was not seen in men |

| ID | First author | Country | Year of publication | Type of study | No. of participants | Participants characteristics | Probiotics | Dose | Comparators | Effects of probiotics | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **13** | Meskina E. [38] | Russia | 2021 | Randomized prospective | 100<br>18–60 years | Moderate | *Bifidobacterium bifidum* 1 5108 CFU and 5107 CFU + *Lactobacillus plantarum* 8p-A3 | 3 capsule BD (10 days) | – | – | Patients who consumed the probiotic diarrhea resolved in a shorter time<br>Cough ↓<br>Hyposmia ↓<br>Weakness ↓ |
| **14** | Paparo L. [45] | Italy | 2021 | *In vitro* | – | – | *L. paracasei* CBAL74 | – | Non-fermented milk | IL-6↓<br>IL-15↓<br>VEGFβ↓<br>IL-1β↓ | Milk fermented with the probiotic led to meaningfully decreased in COVID-19 infected human enteric cells. May be caused through modulating ACE2 and inflammatory cytokines |
| **15** | Rather I. [47] | Korea | 2021 | *In vitro* and *in silico* | – | – | *Lactobacillus plantarum* Probio-88 | – | – | Il-6↓<br>IFNα↓<br>IFNβ↓ | *L. plantarum* had a meaningful beneficial effect on preventing the SARS-CoV-2 replication. Seems this ability may be caused by plantarcin E and F |
| **16** | Reiprich A. [48] | Germany | 2022 | *In vitro* | – | – | *Lactobacillus crispatus* DSM25988 | – | – | - | *L. crispatus* had beneficial effect on human cells to eliminate the SARS-CoV-2 virus |
| **17** | Salaris C. [49] | Italy | 2021 | *In vitro* | – | – | *Lacticaseibacillus paracasei* |  | – | IFNα↑<br>IFNβ↑ | *L. paracasei* DG had a strong antiviral effect on SARS-CoV-2 *in vitro* and also decreased the replication of virus<br>*L. parasasei* enhanced the antiviral effect of lactoferrin on SARS-CoV-2 |
| **18** | Soloveva I. [55] | Russia | 2021 | *In vitro* | – | – | *Bifidobacterium bifidum* 1<br>*B. bifidum* 791<br>*Lactobacillus fermentum* 39<br>*L. fermentum* 90 TC-4<br>*Bifidobacterium longum* 379<br>*Lactobacillus plantarum* 8 RA 3 | – | – | – | Among the probiotics of this study only *L. fermentum* 90 TC 4 showed an antiviral effect on SARS-CoV-2 |
| **19** | Veterini A. [59] | Indonesia | 2021 | Case-Control | 30 Healthcare workers, probiotic group: 34.73±5.612<br>Non-probiotic group: 33.47±3.871 | – | – | – | – | – | Cycle threshold value and disease duration were not meaningfully different in two groups<br>Two individuals of non-probiotic group experienced reinfection |
| **20** | Wang H. [62] | China | 2021 | Retrospective cohort | 156<br>Average age: 48.58 | Mild, Moderate, Severe | *(Streptococcus thermophiles + Lactobacillus bulgaricus + Bifidobacterium longum)* tablet | 4 Tabs TDS | COVID-19 medications given to both probiotic and non-probiotic groups | CRP↓<br>prolactin↓<br>lymphocyte count↑<br>Serum albumin↑ | Patients who consumed probiotics COVID-19 test became negative in a shorter time and diarrhea resolved earlier |

**Table 2. Description of the findings reported in eligible studies (continued)**

| ID | First author | Country | Year of publication | Type of study | No. of participants | Participants characteristics | Probiotics | Dose | Comparators | Effects of probiotics | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Wang Q. [63] | China | 2021 | RCT | 200 Healthy Healthcare workers, probiotic group: 36.13±8.62<br>Non-probiotic group: 35.74±8.88 | – | *S. thermophiles* ENT-K12 | 1 tablet BD (for 30 days) | – | – | Consumption of probiotics as prophylaxis in healthcare workers who had close contact with COVID-19 patients:<br>Respiratory tract infection↓<br>Need for medications (antiviral, etc.) during COVID-19 disease↓<br>Days needed to stay home during disease↓<br>Duration of disease↓ |
| 22 | Wischmeyer P. [64] | USA | 2022 | RCT | 182 | – | *Lactobacillus rhamnosus* GG | – | Placebo | – | Consumption of probiotics in individuals who had close contact with COVID-19 patients was linked to a longer period for symptoms to appear and probiotic group experienced fewer symptoms |
| 23 | Zhang L. [67] | China | 2021 | Cohort | 375<br>Probiotic group: 36–59<br>Non-probiotic: 36–62 | Mild, Moderate, Severe | (*Lactobacillus* + *Entrococcus* + *Bifidobacterium*) capsule | 630 mg BD (3 capsules BD) | COVID-19 medications was given to both probiotic and non-probiotic groups | – | Probiotic consumption was linked to:<br>Length of hospitalization↓<br>Shedding of virus↓<br>Fever duration↓ |

## Discussion

The aim of this systematic review was to investigate the effect of probiotics on COVID-19. The results of this review are based on 23 studies that used various study designs. The findings suggest that the greatest impact of probiotics on COVID-19 is related to controlling inflammation, reducing mortality and morbidity by strengthening and regulating the immune system. Additionally, some probiotics may play an effective role in controlling the symptoms and severity of COVID-19, which will be detailed below.

Previous studies have demonstrated that generally probiotics are complementary options for the treatment and prevention of viral and bacterial infections. Probiotics have also been shown to exert anti-viral effects via diverse mechanisms such as: regulation and modulation of innate and adaptive immune system, maintaining gut and lung mucosal integrity, as well as inhibiting and binding to opportunistic pathogens [27, 50, 61]. Regarding upper respiratory tract infections (URTIs), one meta-analysis of RCTs with 3720 cases showed that patients undergoing probiotics treatment had two-times lower odds of developing URTIs [23]. Regarding lower RTIs, another meta-analyses of RCTs with 2000 patients showed that probiotic use can significantly decrease the ventilator-associated pneumonia incidence [13, 57]. Further, a large meta-analysis of 52 articles stated that probiotics were strongly efficient in the prevention or treatment of acute RTIs [33].

Regarding the effects of probiotics on COVID-19, many studies have shown gut dysbiosis among COVID-19 patients such as alterations in *Bifidobacterium* and *Lactobacillus*. Therefore, probiotic implementation, specifically with these strains, may lead to beneficial outcomes when managing this disease [18]. In one systematic review, probiotic use was suggested to improve host immune response against COVID-19 by three possible mechanisms. These include altering the level of interleukins (IL), virus titers reduction, and interferon and antibody production [39]. Moreover, a review by Batista et al. proposed that probiotic consumption can ameliorate COVID-19 symptoms via regulating, and boosting an individuals' immune response, and improving their gut microbiota in favor of protective microflora [10]. Authors from another review suggested that immune system improvement against COVID-19 can be achieved via intestinal microbiota profile enhancement by probiotic use [2]. Similarly, a study that included a large online cohort of 445 850 individuals, documented that women who consumed probiotics, Omega-3 or Vitamin-D were less infected by SARS-CoV-2, although this was not the case among males [34].

Seven studies included in the present review mentioned *Bifidobacterium* solely or in combination with other bacteria as the studied probiotic [38, 67, 14, 26, 53, 55, 62]. Two studies reported shorter hospitalization periods in the *Bifidobacterium*-receiving group [14, 67]. Bozkurt et al. investigated mild to moderate COVID-19 cases and found that chest CT scan resolved faster, and lower mortalities occurred among patients receiving *Bifidobacterium* compared to patients treated with anti-ILs or antibiotics [14]. They also stated that probiotics use decreased IL-6 levels [14]. Moreover, Zhang et al. in their study among mild, moderate, and severe cases of COVID-19 found that consumption of probiotics composed of *Lactobacillus, Entrococcus*, and *Bifidobacterium genera* was associated with reduced length of hospitalization, virus shedding, and fever duration [67]. Previous studies have demonstrated that loss of *Bifidobacterium* in the elderly is associated with chronic diseases [29]. In addition, one review investigated the possible effects of probiotics, and signified that *Bifidobacterium longum* MM-2, *Bifidobacterium longum* BB536, B*ifidobacterium animalis* ssp. *lactis* (BB-12®), *Bifidobacterium longum* SPM1205, and SPM1206, and *Bifidobacterium longum* SP 07/3 and *B. bifidum* MF 20/5 are among probiotics strains that possess anti-viral features. These results were found in both *in vitro*, and *in vivo* studies as follows, suppressing uncontrolled inflammatory response, reducing virus proliferation in the lungs, increasing adaptive immune response to vaccines, and reducing episodes and severity of URTIs. In addition, many studies on *Bifidobacterium* indicate that this strain may be considered as a complementary therapeutic agent in suppressing cytokine storm, and uncontrolled inflammatory response in COVID-19 patients [12, 19, 42]. Therefore, *Bifidobacterium* appears to be helpful in combating COVID-19 infection via numerous mechanisms.

In terms of signs and symptoms of COVID-19, four studies reported that probiotics use was efficient in relieving diarrhea, cough, anosmia, weakness, preventing nosocomial diarrhea, and decreasing secondary infection [26, 38, 53, 62]. Ivashkin et al. in their RCT reported that despite relieving GI symptoms, probiotics had no meaningful effect on COVID-19 severity. Other similar studies have also reported consistent results, and reported that probiotics use is a beneficial tool for treating gut dysbiosis and improvement of GI symptoms [52]. One study reported that by using a combination of *Bifidobacterium*, *Lactobacillus*, *Enterococcus*, and *Bacillus* tablets, a better immune function and reduced secondary bacterial or fungal infection can be achieved [32]. Moreover, one large systematic review among COVID-19 patients indicated that consumption of probiotics, prebiotics, and synbiotics, via gut/lung microbiome modulation, can shorten disease duration, and decrease its severity of symptoms including fatigue, anosmia, dyspnea, nausea, vomiting and other GI symptoms [65].

With the renowned systemic inflammatory response triggered by SARS-CoV-2, the physiological balance of the gut-brain, gut-heart, and gut-lung axis gets disrupted [11]. Thus, adequate metabolic modulation and preservation of the microbial diversity may be an additional tool to enhance innate immunity and positively modulate the inflammatory response. In a recently published review [56], Spagnolello et al., elegantly summarized the existing evidence around the onset of microbial intestinal dysbiosis in patients with COVID-19, linking the disruption in the normal intestinal flora to a dysregulated immune response [46]. Indeed, the COVID-19 infection was proven to last for a longer period of time in patients with a history of various gastrointestinal diseases [44]. Although the exact pathophysiology of this process remains unknown, potential explanatory models have been recently illustrated [60]. The process may lay in its foundation on the activation of the ACE2 receptors on the intestinal mucosa, which induces enteritis, alteration in the local T cells and B cells response, and eventually inflammatory diarrhea.

Various *in vitro* studies have tried to probe the positive effects of probiotics in normalizing or attenuating inflammatory responses [17, 45, 47, 48, 49]. Ezzat et al. [17] showed that a combination of *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* have meaningful antiviral effects on SARS-CoV-2. This highlights the positive effect of this probiotic polysaccharide made of D-fructose units in COVID-19 modulation, in addition to its renown roles [51]. Similarly, another *in vitro* study [45] showed that non-fermented milk subsequently fermented with the probiotic *L. paracasei* could significantly decrease the number of human enteric cells infected by the SARS-CoV-2 virus and led to lower levels of IL-1-beta, IL-6, IL-15, and Vascular Endothelial Growth Factor (VEGF) beta. Three additional *in vitro* studies [47, 48, 49] elucidated a similar role of other *Lactobacillus* species. Specifically, *Lactobacillus plantarum* was proven to have a meaningful effect on preventing the replication of the SARS-CoV-2 virus, probably by the means of plantarcin E and plantarcin F [47], while *Lactobacillus crispatus* (i.e., DSM25988) was proven to have a beneficial effect on human cells in the process of eliminating the SARS-CoV-2 virus [48]. Finally, *Lactobacillus paracasei* was shown to have strong antiviral effects on the SARS-CoV-2 virus by decreasing the replication of the virus per se and by enhancing the antiviral effect of lactoferrin [49]. Analogous positive effects have also been conceptually confirmed by an *in silico* study by Alam et al. showing that bacterial compounds extracted from *Bacillus* species may represent a potential source of SARS-CoV-2 protease inhibitors [3]. *In vitro* and in silico studies are therefore providing an increasing body of molecular evidence in support of the role of probiotics in both counteracting the life cycle of SARS-CoV-2 and modulating the relatedinflammatory response [43].

When moving from the bench to the bedside, a handful of RCTs have recently investigated the effects of certain probiotics on COVID-19 infections [16, 21, 22, 31, 63, 64]. While a variety of different probiotic types and dosages were used, thus hindering any chances of drawing meta-analytic comparisons, few considerations can be made from their results, leveraging the rigorous methodology of clinical trials. Gutierrez-Castrellon et al. [21] enrolled 300 patients with mild to moderate COVID-19 infection and supplemented them with a mix of probiotics (e.g., *Pediococcus acidi lacti*, *Lactiplanti bacills plantarum*, etc.). When compared to placebo, they reported that probiotics could shorten the duration of COVID-19-related symptoms in enrolled patients, as well as decrease the radiologic burden of disease when assessed by CT imaging. The authors speculated an association between their clinical findings and the detection of higher levels of virus-specific IgM and IgG, lower levels of high-sensitivity C-reactive protein, and overall lower levels of nasopharyngeal viral load, which are renown proxy of inflammatory response and burden of disease in COVID-19 patients [58].

Another RCT reported significantly higher remission rates among a probiotic group compared to a placebo group (53.1% vs 28.1%). [20] The results from this RCT also found that treatment was linked to lower nasopharyngeal viral load, pulmonary infiltrations, and shortened duration of symptoms, compared to a control group [20]. Another RCT demonstrated that probiotics were able to modulate the immune performance, and decrease secondary infection [32]. Moreover, in terms of COVID-19 prevention, many studies have shown that probiotics can block the Angiotensin-Converting Enzyme (ACE) receptor by binding to active sites, and thus act as a possible preventive measure against SARS-CoV-2. Also, probiotics in foods, such as dairy products can exert a potentially efficient impact to prevent COVID-19. Extensive research among infants, children, adults, and people of older age have shown that probiotic-containing fermented milk significantly reduces the incidence of URTIs [35, 37].

Analogously, Wischmeyer et al. investigated the protective role of *Lactobacillus rhamnosus* [64]. They enrolled 182 individuals who were self-identified as close contacts of SARS-CoV-2-positive patients. The researchers found that those who received *Lactobacillus* and eventually contracted COVID-19 had a prolonged latency for symptoms onset and milder symptoms compared to the placebo group. This allowed the research group to add to the existing literature on the topic [30] by hypothesizing an effective role of probiotics in the early phases of the COVID-19 infection, from the first contact to onset of typical symptoms. Interestingly, a similar clinical trial has been tailored to healthcare providers and first responders, who are at close contact with COVID-19 patients. Wang et al. [63] showed that the administration of one tablet of *S. thermophiles* (ENT-K12) daily for a 30-day timespan was associated with an effective prophylaxis, leading to a lower rate of respiratory tract infections, lower number of prescribed medications in the patients who eventually became infected, as well as a shorter recovery.

There is a growing body of clinical studies and RCTs supporting consumption of probiotics for the prevention and supportive treatment of patients with the SARS-CoV-2 infection. The pleiotropism of available probiotics may enhance the process of strengthening biological barriers in the gastrointestinal tract and facilitate the homeostasis within the normal flora. In spite of the enthusiasm that surrounds the adoption of probiotics in this setting, a word of caution is warranted. Specifically, three adverse reports have been recently published showing that the efficacy and safety of certain probiotics (e.g., *Salmonella enterica, Lactobacillus acidophilus*, and *Bacillus clausii*) in this setting is contentious [30].

## Conclusion

To date, the fight against COVID-19 causes and requires more interventions to manage it. Related interventions and prevention of new cases places large economic burdens on governments, and effective interventions can make disease control possible. Therefore, probiotics intake could be a complementary strategy to effectively control the disease along with the vaccines, due to their antiviral properties and their metabolites. Probiotics are considered an anti-COVID-19 strategy because of its effect on ameliorating gut microbiota and boosting response of immune host. Additionally, probiotics reduce the risk of secondary infection by making immune function moderate. Available evidence on probiotics can be utilize as a valuable source for investigating the antiviral role of probiotics in related research studies. In this review, the antiviral potential of *Lactobacillus paracasei* metabolite PlnE and PlnF against SARS-CoV-2 was found. Other and new types of probiotics may be considered for health promotion, disease prevention, and treatment of various diseases. More studies are needed to investigate the relationship between probiotics and the management of COVID-19.

## Declarations

**Ethics approval and consent to participate.** Not applicable.

**Consent to publication.** Not applicable.

**Availability of data and material.** The authors stated that all information provided in this article could be shared.

**Competing interests.** The authors declare that there is no conflict of interest regarding the publication of this manuscript.

**Funding.** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Acknowledgments.** The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Research Center for HIV/AIDS, Tehran University of Medical Sciences, and the University of Sydney.

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Поступила в редакцию 14.01.2023
Принята к печати 23.06.2023

Received 14.01.2023
Accepted 23.06.2023