Probiotics and Their Conceivable Part within the Avoidance or Treatment of Covid-19: A Systematic Review

Mojtaba Hajipour[1], Fateme Moghbeli[2*], Mahla Chambari[1]

1. Department of Nutrition Sciences, Varastegan Institute for Medical Sciences, Mashhad, Iran.
2. Department of Health Information Technology, Varastegan Institute for Medical Sciences, Mashhad, Iran.

A R T I C L E I N F O	A B S T R A C T
	Introduction: Today, the use of probiotics is very popular among the public, which has recently been tested in COVID-19. The aim of this study was to collect all studies related to the immune effects of probiotics and their possible role in the prevention or treatment of COVID-19 achieve a comprehensive result.
	Method: The article is a systematic review that uses the PRISMA checklist to extract articles. After searching for the keywords probiotics, treatment, prevention, coronavirus, and covid-19 and combining them in databases (Google Scholar, PubMed, and Science Direct) according to the inclusion and exclusion criteria, 18 articles were finally reached. Therefore, the articles of the last 10 years (2012-2012) that have been scientifically published in databases were qualitatively analyzed by reviewing both authors.
	Results: Through the qualitative analysis of most articles, we can mention that the modulation of the gut or lung microbiome is an adjuvant treatment or prevention of COVID-19, due to the immunomodulating properties of probiotics. As well as, based on the results of these articles, probiotics can be effective in reducing the secondary infection caused by Covid-19, modulating the inflammatory response, and reducing the duration of the disease. In addition, the administration of probiotics can be useful as an alternative to ameliorate COVID-19 disease and increase the effectiveness of the vaccine.
	Conclusion: Based on the evidence, probiotics boost the immune system and could be useful in the prevention or adjunctive treatment of COVID-19. More randomized trials are required to support these findings.

Introduction

The coronavirus caused by the coronavirus SARS-CoV-2 originated in Wuhan, China (1) and spread around the world in December 2019 so fast, (2) Coronaviruses are a group of viruses that are responsible for a wide range of diseases.

Diverse sorts of human coronaviruses cause different respiratory infections, for case in powerless cases side effects such as colds and in other more extreme cases indications such as pneumonia, bronchitis, intense respiratory disorder (3). In this regard, infection can be Asymptomatic until severe symptoms vary.

May moreover influence the gastrointestinal tract, liver, and anxious framework (4). Due to the high cost of vaccines and the low availability of vaccines in many countries, therapeutic interventions that can prevent the disease or reduce the symptoms of the disease are of great importance.

Clinical perceptions of individuals with COVID-19 amid plagues around the world appear that the elderly and individuals with conditions such as diabetes mellitus, high blood pressure, cardiovascular illness, and cancer are more likely to create Corona illness and indications. They are more severe and the mortality rate is higher in these people, which shows the role of the immune system in COVID-19 (5).

The gastrointestinal tract is the body's largest immunological organ, with trillions of microbes residing in the gastrointestinal tract. Digestion can strengthen the immune system. One of the suggested mechanisms for this is that probiotics promote intestinal health and maintain the body's ecological balance, and reduce the severity of diarrhea by strengthening the intestinal flora and inhibiting harmful bacteria (6).

Current evidence suggests that the gastrointestinal microbiome may regulate the stimulation or suppression of invasive viruses, and that some gastrointestinal bacteria may

* *Corresponding author:* Fateme Moghbeli, Associate Professor, Department of Health Information Technology, Varastegan Institute for Medical Sciences, Mashhad, Iran. Tel: +989153094230, Email: moghbelif@varastegan.ac.ir.

protect the body against pathogens by interacting with human cells and enhancing positive immune responses, as well as probiotics. They reduce the number of viruses in the body and thus reduce the symptoms of viral colds, and this mechanism can also be attributed to the corona virus (7, 8).

In January 2020, the International Health Committee of China and the Guidelines of Traditional Chinese Medicine proposed the probiotics use to treat patients with COVID-19 disease to modulate the microbial flora and prevent secondary infections (9). Probiotics also increase the immunity of the host by modulating the TH1 / TH2 (T helper type 1 / T helper type 2)

ratio and have a protective effect on pathological diseases (10).

Also, the use of probiotic supplements along with vitamin D and zinc reduces the T1 / T17 ratio and pro-inflammatory factors such as IL6, IL8 and TNFα, thereby reducing inflammation of the lungs and airways in patients with COVID -19.

So far, no definitive method has been found for the prevention or cure of COVID -19 due to the lack of scientific evidence and clinical trials, and it can be said that probiotics have a possible role in the adjunctive treatment or prevention of COVID -19. The goeal of this study was to gather all papers related to probiotics and their possible role in the prevention or adjunctive treatment of COVID -19 and achieve a comprehensive result.
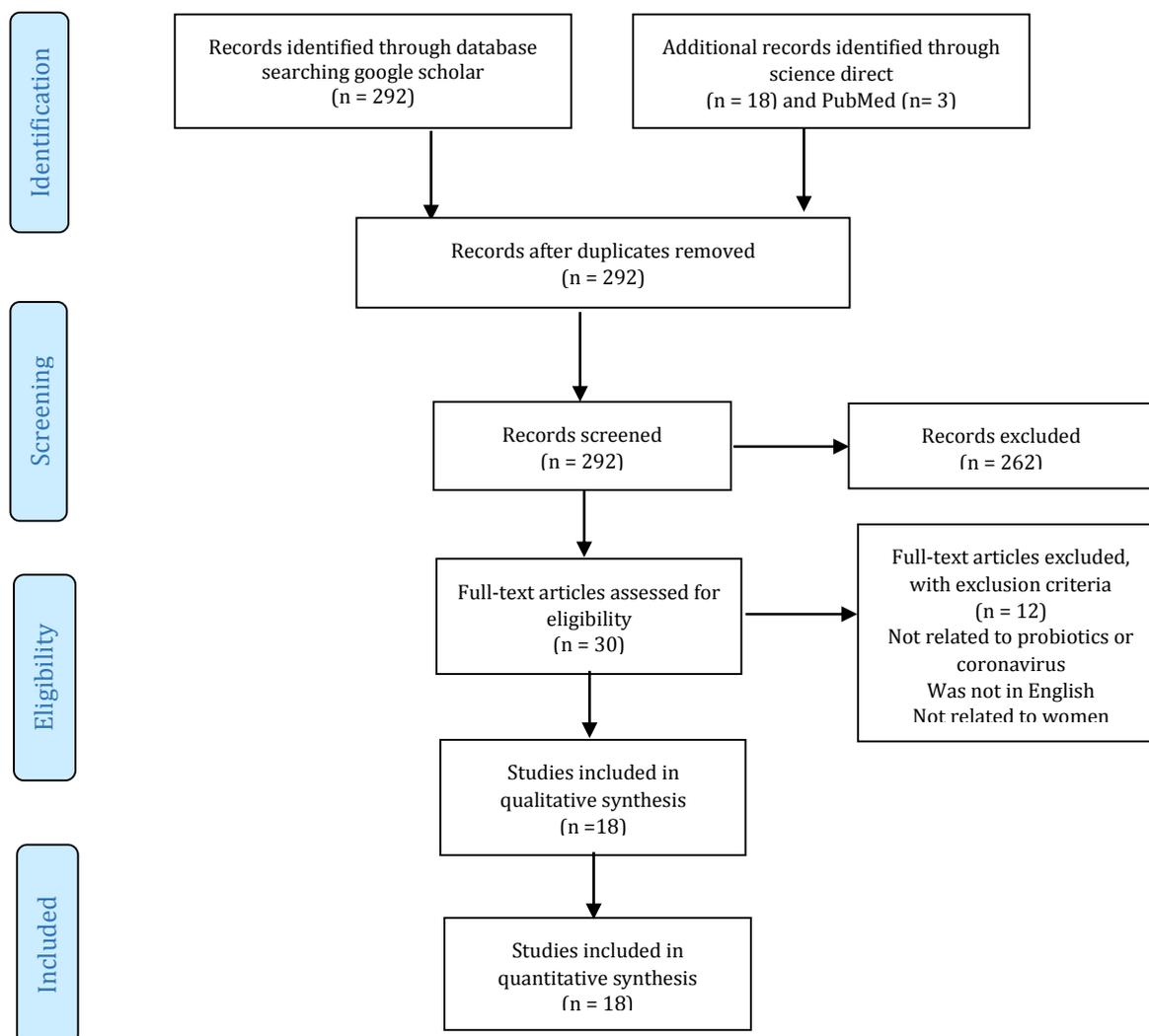

Figure 1. Article selection chart based on PRISMA checklist

Materials and Method

The strategical method followed the guidelines established through PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (11).

Searching the keywords Probiotics, Treatment, Prevention and covid-19 and coronavirus first, and combining the keywords in the Google Scholar, PubMed and Science Direct databases in the period October 2012 to October 2022, a total of 313 articles in English were retrieved found. extract. Articles were judged on title, abstract, and body content to ensure their relevance to the prevailing research. Two independent authors conducted Data extraction, and articles indexed in two or more databases were considered only once. Then, the outcomes were checked by a third researcher to make sure that each one the eligible papers have been evaluated. Finally, 18 articles were included in the study.

The extracted data was organized by author's name, country, publication date, type of clinical trial, sample size, diagnostic criteria, patient characteristics, study duration, type and strain of probiotics used, dose of probiotics used, and positive treatment outcomes.

The inclusion criteria were: (i) articles in the period 2011-2021; (ii) access to the full text; (iii) articles in English; and (iv) clinical trial studies.

The exclusion criteria were: (i) congress papers; (ii) Irrelevant Articles not to pay attention to coronavirus; (iii) Irrelevant Articles not to pay attention to probiotics; (iv) non-English papers; and (v) studies without clear information.

Figure 1 shows the study selection chart.

Results

Probiotics can be effective in reducing the secondary infection of COVID 19, modulating the immune system and inflammatory response, as well as reducing the duration of the disease.

Based on the results of these articles, the administration of probiotics can be useful in the viral respiratory infections (VRIs) prevention, including COVID-19, and Probiotic adjuvant therapy may be considered as an alternative way to progress or prevent COVID-19 disease. Finally, the probiotic bacteria use against COVID-19 is practical, both in terms of vaccination and treatment. Many probiotics have been approved to decrease the bacterial or viral infections duration. Table 1 shows 18 relevant articles on probiotics and their effects in COVID-19 patients.

Discussion

Qiang Li et al., showed a total of 93 out of the 123 patients (75.61) were cured by probiotics and had a median 32-day hospital stay and an average virus clearance time of 23 days, which was significantly longer than patients without probiotics, were discharged from the hospital (12).

Dynamic changes of 8 chosen laboratory variables (C-reactive protein (CRP), total T lymphocytes, IL-6, NK cells, T4 CD4 + cells, B lymphocytes, CD8 + T cells and CD4 / CD8 ratio) were monitored and as a result, the probiotics could not increase IL-6 levels but could modulate immunity and decrease the secondary infection rate in COVID-19 patients (27).

Bozkurt et al., showed that given the close association between virus replication and gastrointestinal immunity, a probiotic strategy that targets and modulates the immune response can be useful in decreasing virus replication (13). The known anti-inflammatory activity of some bifidobacteria suggests that these bacteria may play a useful role in showing the inflammatory response, which appears to be highly virus-specific. New approaches to the use of certain probiotic drugs are promising both for preventing the immune response against the virus and improving the efficacy of vaccines. (28).

Olaimat et al. reported that probiotics may decrease the incidence and severity of illnesses and can be effective in the COVID-19 adjunctive treatment or prevention. Probiotics may even prevent COVID-19 by preserving the human gastrointestinal tract or lung microbiota because dysbiosis plays an important role in susceptibility to infectious diseases. In addition, they reported that laboratory and clinical studies are needed to assess the potential prophylactic and therapeutic effects of probiotics against SARS-CoV-2 infection (14).

According to the article, the use of probiotics can reduce the tendency of viral invasion by improving the epithelial barrier ACE2. Antimicrobial peptides or bacteriocins released by beneficial bacteria, SCFAs and ACE inhibitory peptides can balance the dysregulated RAS. Therefore, blood pressure or cardiovascular complications may decrease (22, 29).

Table 1. Relative articles on probiotics based on PRISMA chart

Row	Reference	Positive results
1	(12)	• Immune response modulation • Reducing the rate of secondary infection.
2	(13)	• Immune response modulation • Increasing the effectiveness of the vaccine
3	(14)	• Reducing the incidence and severity of the disease • Prevention of COVID-19 by preserving the human gastrointestinal tract or lung microbiota
4	(15)	• Prevention of VRIs • Increasing the effectiveness of the vaccine • Use as an adjunctive therapy
5	(16)	• Reducing the tendency of the virus to enter the body by improving the epithelial barrier containing angiotensin-converting enzyme 2 (ACE2) • Balancing dysregulated renin-angiotensin system (RAS) by releasing antimicrobial peptides or bacteriocins, Short-chain fatty acids (SCFAs), and ACE inhibitory peptides • Balancing the levels of pro- and anti-inflammatory cytokines and increasing the number of T cells • Hyaluronan degradation and improvement of acute respiratory distress syndrome (ARDS)
6	(17)	• Modulating immune responses, maintaining intestinal homeostasis and interferon production • Suppression of virus-induced cytokine storm • Reduction of ventilator-associated pneumonia in patients • Overcoming intestinal dysbiosis induced by SARS-CoV2 infection • Increase the body's immune resistance
7	(18)	• Use as an adjunctive therapy that is safe, inexpensive, commercial, and readily available
8	(10)	• Modulating the immune response and reducing the cytokine storm generated during COVID-19 infection • Balancing gut microflora composition, improving gut barrier function and protective immune responses
9	(19)	• Reducing the symptoms of upper respiratory tract infections • Use as an adjunctive therapy
10	(20)	• Boosting the body's immunity • Reduction of disease symptoms
11	(21)	• Increase the body's immune resistance • Balancing gut microflora composition, improving gut barrier function and protective immune responses
12	(22)	• Use as an adjuvant treatment and reducing inflammatory complications
13	(23)	• boosting the function of natural killer cells • Stimulation of IgA antibodies • Control of mucosal barrier inflammation • Strengthening immunity
14	(8)	• Strengthening intestinal and lung immunity • Reduce intestinal inflammation • Reducing the intensity and duration of the infection
15	(24)	• Boosting the immune response by modulating gut microbiota in the lung • Inhibiting virus replication in the lung by releasing metabolites (such as butyrate, desaminotyrosine, and secondary bile acids)
16	(25)	• Enhancement of innate and acquired immune responses • Reduction of complications of VRI • Reduction of disease severity in VRIs
17	(26)	• Modulation of the immune system
18	(6)	• Adjunctive therapy to improve the immune system • Attenuation of virus replication • Helping to treat COVID-19

Reducing NO production can reduce cellular oxidative stress. This can lead to misregulation of inflammatory pathways (NLRP3 and NF-κB) and ultimately the secretion of cytokines or pro-inflammatory chemokines. Probiotics and bacteriocins can balance the levels of anti-inflammatory and anti-inflammatory cytokines and increase the number of T-cells in SARS-CoV-2 patients. Probiotics can reduce hyaluronic acid, improve ARDS (14, 30).

Conclusion

probiotic and its probable role in COVID-19 prevention or adjunctive cure were described, which affect gastrointestinal health by modulating the gut microbial flora. Since 5-10% of covid-19 patients have symptoms like vomiting, diarrhea, nausea, and abdominal pain, we believe that viruses affect the microbiome. Thus, alterations in the gut microbiome led to more severe disease and poor treatment outcomes. According to the review of various studies, we found that probiotics bolster the immune system.

In addition, they prevent the reproduction of pathogens and help create a stable and balanced microbial environment in the body, increasing the population of beneficial bacteria. Due to the different therapeutic effects of different probiotic bacteria, the strains and effective doses in the treatment of each disease should be determined so that probiotics can be used as adjunctive therapy along with the common treatments of Covid-19 diseases. Therefore, Randomized trials with a more appropriate design are needed in this field.

Acknowledgements

Conflict of Interest

There is no conflict of interest to declare.

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