Efficacy of Nutraceuticals (probiotics or prebiotics or synbiotics) in the prevention or treatment of COVID -19: A systematic review and meta-analysis

Funded by:
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Declaration

This work is a result of a grant award received from ILSI India in response to a call for proposals on Systematic Reviews and Meta-analysis on Nutrition and Immunity with specific reference to Covid 19.

Contents

Background

- Despite the high prevalence of COVID-19, effective medicines or therapies remain few, and no definite pharmaceutical treatment is available to target the disease's relevant components.
- Probiotics have gained the interest of clinicians for their applicability in the prevention and treatment of multiple ailments.

- Several studies have demonstrated the positive and encouraging effects of probiotics, prebiotics, or synbiotics in the treatment or prevention of COVID-19.
- Their safety and effectiveness in Covid-19 patients have not been systematically reviewed.
- There is a need to synthesize the evidence to determine if nutraceuticals can be used to prevent or treat COVID-19

Objective & Research Question

Objective: To assess the safety and efficacy of Probiotics, Prebiotics, or Synbiotics) in preventing or treating COVID-19

Research Question: Whether administration of nutraceuticals along with standard care is safer and more effective as compared to standard care alone in the prevention and treatment of COVID-19?

Eligibility Criteria

	Inclusion	Exclusion
Types of studies	RCTs, quasi-experiments, one-arm trials, pre-post studies, and other experimental study designs	Case reports, observational studies, clinical observations, grey literature, reports, abstracts, or conference proceedings
Types of participants	Affected/exposed to COVID-19 infection, regardless of age, gender, ethnicity, and setting	Severely ill patients
Types of interventions	Supplementation of nutraceuticals as an adjunct to standard treatments, irrespective of form, dose, duration, or frequency, other adjunct interventions to the standard treatment (such as ozone oxygen therapy)	Supplementation of adjunct other than nutraceuticals
Types of comparison	Standard of care without supplementation of nutraceuticals, or any active comparator (such as appetizers, nutritional supplements, etc	-

Types of outcome measures

Primary outcomes

1. Number of cases of COVID-19 (dichotomous outcomes)
2. Change in disease severity (dichotomous outcomes)
3. Days of hospitalization (continuous outcomes)

Secondary outcomes

1. Number of deaths(dichotomous outcomes)
2. Adverse events (dichotomous outcomes)
3. Free of fatigue (Post-Covid Fatigue) (dichotomous outcomes)

Methods

Search methods

- We searched the following databases:
  - MEDLINE (via PubMed)
  - The Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library; 2021, issue 9)
  - Web of Science & Google Scholar
  - WHO Covid-19 database (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/)
- Clinical trial registries
  - WHO International Clinical Trials Registry (ICTRP) (apps.who.int/trial search/)
  - clinicaltrials.gov (www.clinicaltrials.gov) for ongoing trials.
- WHO Regional Journals databases from Latin America, Africa, and South-East Asia
- Websites, and e-libraries of development agencies
  - WHO Department of Nutrition for Health and Development
  - UNICEF
  - Nutritional International
  - International Food Policy Research Institute (IFPRI)
- Additionally, we checked the reference lists of reviews and retrieved articles.

- We considered including studies between 2019 to 2021
- Last search was performed on December 2021
- Search included relevant keywords, free-text terms, and Medical Subject Headings (MeSH)

Search strategies

Medline via PubMed	CENTRAL via Cochrane Library	WHO Covid-19 databases
(("probiotic*"[Title/Abstract] OR "pro biotic*"[Title/Abstract] OR "prebiotic*"[Title/Abstract] OR "pre biotic*"[Title/Abstract] OR "synbiotic*"[Title/Abstract] OR "lactobacill*"[Title/Abstract] OR "lacto bacill*"[Title/Abstract] OR "bifidobacteri*"[Title/Abstract] OR "bifidus*"[Title/Abstract] OR "streptococcus thermophil*"[Title/Abstract] OR "saccharomyce*"[Title/Abstract] OR "probiotics"[MeSH Terms] OR "lactobacillus"[MeSH Terms] OR "bifidobacterium"[MeSH Terms] OR "streptococcus thermophilus"[MeSH Terms] OR "saccharomyces"[MeSH Terms]) AND ("covid*"[Title/Abstract] OR "corona-virus"[Title/Abstract] OR "corona-virus"[Title/Abstract] OR "cov"[Title/Abstract] OR "ncov*"[Title/Abstract] OR "n cov*"[Title/Abstract] OR "sars*"[Title/Abstract] OR "covid*"[Title/Abstract] OR "covid 19"[MeSH Terms])) AND (2019:2021[pdat])	IDSearch #1 covid* #2 corona* #3 n-cov* #4 ncov* #5 sars* #6 MeSH descriptor: [COVID-19] explode all trees #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 probiotic* #9 "pro biotic*" #10 pro-biotic* #11 prebiotic* #12 "pre biotic*" #13 pre-biotic* #14 synbiotic* #15 lactobacill* #16 bifidobacteri* #17 bifidus* #18 "streptococcus thermophil*" #19 saccharomyce* #20 MeSH descriptor: [Probiotics] explode all trees #21 MeSH descriptor: [Prebiotics] explode all trees #22 MeSH descriptor: [Synbiotics] explode all trees #23 MeSH descriptor: [Lactobacillus] explode all trees #24 MeSH descriptor: [Bifidobacterium] explode all trees #25 MeSH descriptor: [Streptococcus thermophilus] explode all trees #26 MeSH descriptor: [Saccharomyces] explode all trees #27 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 #28 #7 AND #27	tw:(probiotic* OR prebiotic* OR synbiotic* OR lactobacill* OR bifidobacteri* OR bifidus* OR "streptococcus thermophil*" OR saccharomyce*) AND type_of_study:("clinical_trials") AND la:("en")

Methods

Selection of studies, data extraction, Risk of Bias assessment

Screening and Selection of studies

- After removing duplicates, two investigators independently screened all articles retrieved from searches using Covidence screening tool in two phases.
  - First phase: Based on titles and abstracts.
  - Second phase: Based on full texts
- Disagreements were resolved by consensus.
- Flow of studies was recorded in PRISMA-flow diagram

Data extraction and management

- Data was extracted using a pilot-tested data extraction form, including study design, country, sample size details, characteristics of study participants, intervention details, dependent variables, and funding sources

Risk of Bias assessment

- Two investigators assessed the risk of bias for RCTs using the RoB2 tool & ROBINS-I tool for non-RCTs.
- Discrepancies amongst investigators were resolved through consensus.

Methods

Meta-analysis

Measures of treatment effect

- Meta-analysis was undertaken using Review Manager 5
- For dichotomous outcomes, we expressed results as risk ratios (RRs) with 95% confidence intervals (CIs).
- We had planned to use mean differences or standardized mean differences with 95% CIs to express continuous variables
- For each outcome, we examined reported effect sizes and heterogeneity across studies.
- When data were insufficient, we provided a narrative description of results.

Unit of analysis issues

Individual participants in each clinical trial

Assessment of heterogeneity

- We had planned to assess statistical heterogeneity using I^2 with a P-value ≤ 0.1 as statistically significant and to explore possible reasons for heterogeneity.
- However, we found only one study addressing each outcomes. Hence, issue of heterogeneity did not arise.

Methods

Grading the Quality of Evidence

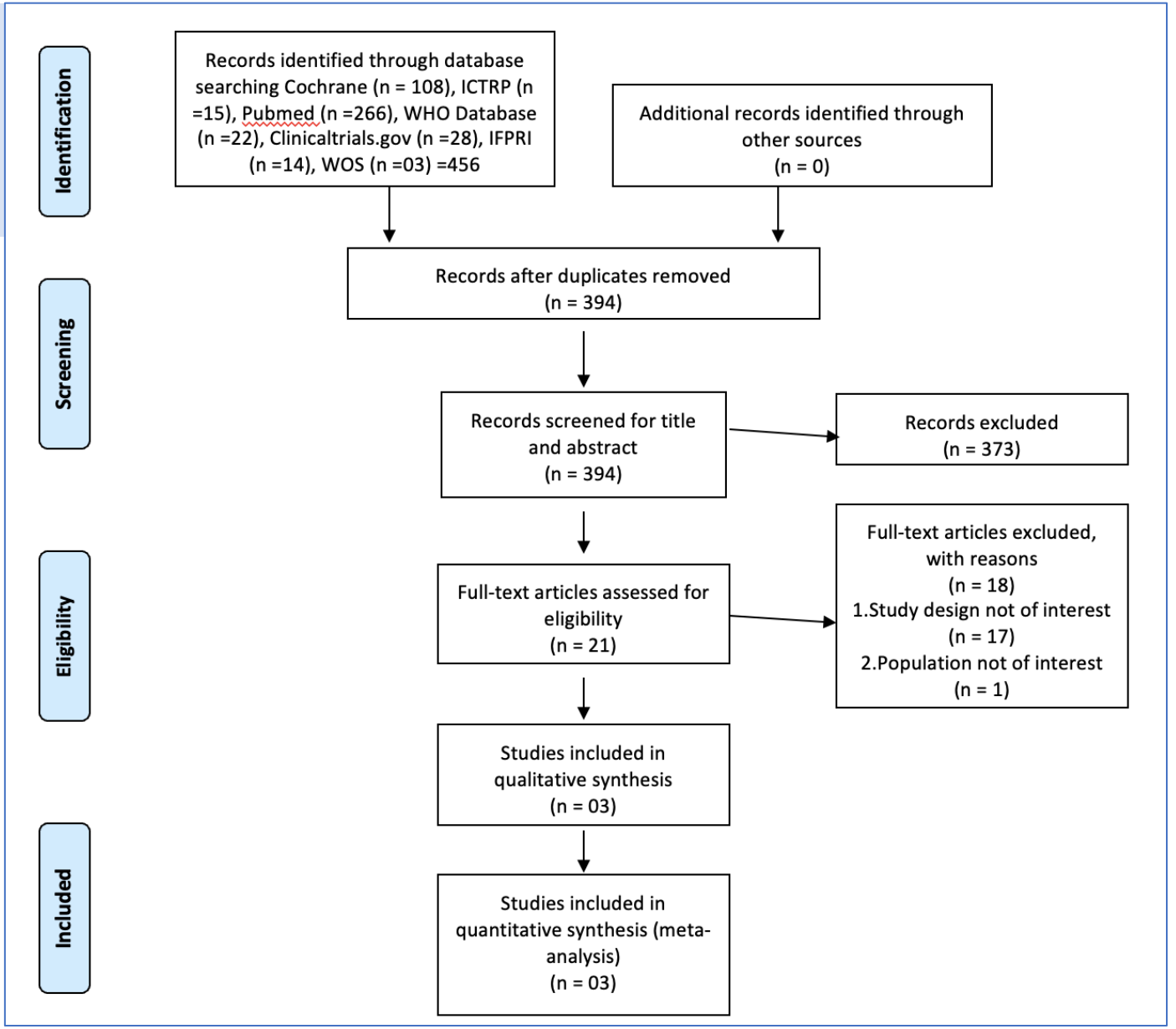
Summary of findings tables

- Two reviewers independently assessed certainty of evidence using GRADE approach as:
  - High certainty: We are very confident that the true effect lies close to the estimate of the effect.
  - Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
  - Low certainty: Our confidence in the effect estimate is limited: the true effect may differ substantially from the effect's estimate.
  - Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
- We reported an overall assessment of certainty of evidence for following outcomes
  - Number of deaths
  - Number of adverse events
  - Days of hospitalizations

Results

Results of the search

- We identified 456 potential studies
- After removing duplicates, two reviewers independently examined 394 studies and removed 373 studies.
- We then independently assessed full texts of 21 studies and excluded 18 studies
- Only three studies were included in meta-analysis



Results

Characteristics of included studies

- Total number of participants included in three trials: 428
- In two trials, probiotics were used as an adjuvant treatment to the standard care, and in one trial, probiotics were given as an adjuvant to the immuno-booster.
- None of the included studies reported the number of cases of COVID-19 and changes in the disease severity.
- Outcome measures were mainly focused on the number of deaths, adverse events and days of hospitalization.

Results

Characteristics of included studies

Review ID (Country)	Study Design	Sample size details	Characteristics of study participants	Intervention Details	Comparison group	Outcomes
Araimo et al., 2021 (Italy)	Single centric, open, RCT. (NCT04366089)	**Total**: 28 IG: 14 CG:14	**Age (Mean ± SD):** IG: 63.3 ± 12.2 years CG: 60.1 ± 14.4 years **Male/Female ratio:** IG: 9/5 CG: 7/7	SC (referred to as 'ad interim BAT: antibacterial + antiinflammatoryanti-cytokineine) + Probiotics (SivoMixx* one sachet every 12 h for 7 days) + Oxygen-ozone therapy (5×10^3mcg of ozone for 7 days)	Standard care (referred to as 'ad interim BAT: antibacterial, anti-inflammatory + anticytokine	**Outcomes of interest:** 1.No of Deaths: Day 7, 14, 30 2.Adverse events
Ivashkin et al., 2021 Moscow, Russia Federation	RCT, single-center, open-label trial (NCT04854941)	**Total**: 200 IG: 99 CG: 101	**Age** IG: 65 (59–71) years CG: 64 (54–70) years **Male/Female ratio:** IG: 44/55 CG: 48/53	SC (Dexamethasone + antiviral, antibacterial + anticoagulant + anticytokine) + Probiotics (Lacticaseibacillus rhamnosus PDV 1705, Bifdobacterim bifdumPDV 0903, Bifdobacterim longum subsp. infantis PDV 1911, Bifdobacterium longum subsp. longum PDV 2301) (Dosage: Tds for no more than 14 days)	Standard Care (Dexamethasone + antiviral, antibacterial + anticoagulant + anticytokine	**Outcomes of interest:** 1.Days of hospitalization: 2.No. of deaths n 3.No of adverse events
Abhijit Rathi et al., 2021 India	Randomized, multicentric, double-blind placebo-controlled trial. (CTRI/2021/05/033576)	**Total** 200 IG: 100 CG: 100	**Age (years); SD; Range-** IG: 41.29 ± 13.0 (20–75) CG: 41.17 ± 12.9 (20–75) **Males: Females (%)-** IG: 65:35 CG: 62:38	ImmunoSEB (500 mg/capsule) + ProbioSEB CSC3 (5 billion CFUs /capsule)	Placebo for 14 days	**Outcomes of interest:** **Post Covid -19 Fatigue**

Results

Characteristics of ongoing studies

SNo	Recruitment status	Study Id	Public Title	Date of Registration	Country
1.	Recruitment status completed	NCT04399252	Randomized, double-blind, placebo-controlled trial of Probiotics to Eliminate COVID-19 Transmission in Exposed Household Contacts (PROTECT-EHC): a clinical trial protocol	May 22, 2020	Durham, North Carolina, United States
2.	Recruitment status completed	NCT04621071	Efficacy of Probiotics in Reducing Duration and Symptoms of COVID-19	November 9, 2020	Canada, Quebec
3.	Recruitment status completed	NCT04734886	The Effect of Probiotic Supplementation on SARS-CoV-2 Antibody Response After COVID-19	February 2, 2021	Sweden
4.	Recruitment status completed	NCT04517422	Efficacy of L. Plantarum and P. Acidilactici in Adults With SARS-CoV-2 and COVID-19	August 18, 2020	Mexico
5.	Recruitment status completed	NCT04507867	Effect of an NSS to Reduce Complications in Patients with Covid-19 and Comorbidities in Stage III	August 11, 2020	Mexico
6.	Recruitment status completed	NCT04458519	Efficacy of Intranasal Probiotic Treatment to Reduce Severity of Symptoms in COVID19 Infection	July 7, 2020	Canada, Quebec
7.	Recruitment status completed	IRCT20161206031255N4	Efficacy of prebiotic products on admitted patients with Covid-19	December 7, 2020	Iran
8.	Recruitment status completed	NCT05043376	Study to Investigate the Treatment Benefits of Probiotic Streptococcus Salivarius K12 for Mild-to-moderate COVID-19	September 14, 2021	Pakistan
9.	Recruitment status completed	IRCT20101020004976N6	Investigation of the effect of Lactocare® synbiotic on the prevention of COVID-19 infection in the staff of the emergency department	2020-07-18	Iran

Results

Characteristics of ongoing studies

	Recruitment status	Study Id	Public Title	Date of Registration	Country
10.	Recruiting	NCT05080244	Evaluation of the Efficacy of Probiotics to Reduce the Occurrence of Long COVID	October 15, 2021	Canada, Quebec
11.	Recruiting	NCT04847349	Live Microbials to Boost Anti-Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Immunity Clinical Trial	April 19, 2021	United States, New Jersey
12.	No longer in EU/EEA	2020-001597-30	A study to test the effectiveness and safety of bacteria called Bifidobacterium breve in patients with COVID-19 infections	April 9, 2020	United Kingdom
13.	Recruiting	NCT04937556	Evaluation of a Probiotic Supplementation in the Immune Response of Participants With COVID-19 (Coronavirus Disease)	June 24, 2021	Spain
14.	Not yet recruiting	NCT04907877	Bifido- and Lactobacilli in Symptomatic Adult COVID-19 Outpatients (Pro COVID)	June 1, 2021	Ukraine
15.	Recruiting	JPRN-jRCTs021200020	Study of the additional effect of Kampo medicine on common cold symptoms in COVID-19 patients	August 25, 2020	Japan
16.	Not Yet Recruiting	CTRI/2021/03/031720	The study to explore the effect of Bacillus calusii and Bacillus Coagulans (the Probiotics) on Covid-19 disease progression in addition to routine Covid-19 treatment	March 4, 2021	India
17.	Recruiting	NCT04813718	Post COVID-19 Syndrome and the Gut-lung Axis	March 24, 2021	Austria
18.	Suspended	NCT04793997	Microbiome Therapy in Covid-19 Primary Care Support (MiCel)	March 11, 2021	Belgium
19.	Recruiting	ChiCTR2000029974	A prospective, multicenter, open-label, randomized, parallel-controlled trial for probiotics to evaluate efficacy and safety in patients infected with 2019 novel coronavirus pneumonia (COVID-19)	31 October 2020	China

Results

Characteristics of ongoing studies

SNo	Recruitment status	Study Id	Public Title	Date of Registration	Country
20.	Recruiting	NCT04366089	Oxygen-Ozone as Adjuvant Treatment in Early Control of COVID-19 Progression and Modulation of the Gut Microbial Flora	April 28, 2020	Italy
21.	Recruiting	NCT04666116	Changes in Viral Load in COVID-19 After Probiotics	December 14, 2020	Spain
22.	Not yet recruiting	ACTRN12620000480987	Stress-reduction Using Probiotics to Promote Ongoing Resilience Throughout COVID-19 for Healthcare Workers (SUPPORT COVID-19 Healthcare Workers)	April 16, 2020	New Zealand
23.	Recruitment status completed	IRCT20200318046812N3	Efficacy and safety of "Bio Boost" supplement on the incidence of COVID-19 symptoms of asymptomatic family members of COVID-19 patients	Jan 12, 2021	Iran
24.	Not yet recruiting	NCT04756466	Effect of the Consumption of a Lactobacillus Strain on the Incidence of Covid-19 in the Elderly	February 16, 2021	Spain
25.	Recruiting	NCT04366180	Evaluation of the Probiotic Lactobacillus Coryniformis K8 on COVID-19 Prevention in Healthcare Workers	April 28, 2020	Spain
26.	Recruiting	NCT04941703	"CHANGE COVID-19 Severity"	June 28, 2021	United States, Tennessee
27.	Not yet recruiting	NCT04877704	Symprove (Probiotic) as an add-on to COVID-19 Management	May 7, 2021	United Kingdom
28.	Not yet recruiting	NCT04979065	Nutrition, Immunity, and Covid-19 in Obese People	July 27, 2021	Indonesia
29.	Recruiting	NCT04950803	A Randomised-controlled Trial of an Oral Microbiome Immunity Formula in Recovered COVID-19 Patients	July 6, 2021	Hong Kong
30.	Recruiting	NCT04420676	Synbiotic Therapy of Gastrointestinal Symptoms During Covid-19 Infection	June 9, 2020	Austria
31.	Recruiting	NCT04884776	Modulation of Gut Microbiota to Enhance Health and Immunity	May 13, 2021	Hong Kong

Results

Risk of bias in included studies

One trial was at ‘High risk’ of bias, whereas the other two trials were at ‘Some concerns’ for risk of bias

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Results

Effects of interventions

Comparison 1: Probiotics or prebiotics or symbiotics (as a adjunct to standard treatments) verses Standard of care without supplementation of probiotics or prebiotics or symbiotics

1. Number of cases of COVID-19: We did not find any study that assessed this outcome.

2. Change in disease severity: We did not find any study that assessed this outcome.

3. Days of hospitalization

- Only one study reported data
- Probiotics did not reduce number of days of hospitalization

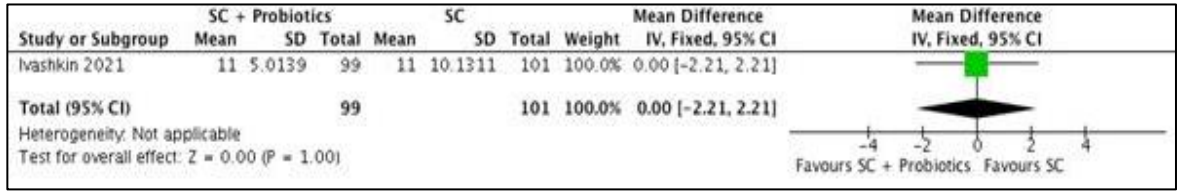


Figure 3: Forest plot of of comparison: SC+ Probiotics versus SC, outcoe: Days of hospitalization

4. Number of deaths

- Only one study reported data
- Risk of death in both groups was same

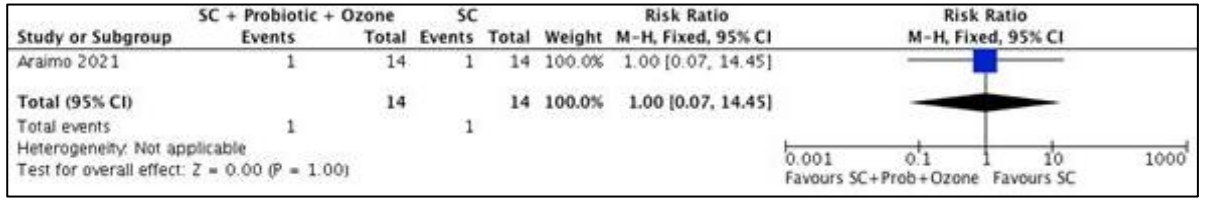


Figure 4: Forest plot of comparison: SC+ Probiotics + Ozone therapy versus SC, outcome: Deaths

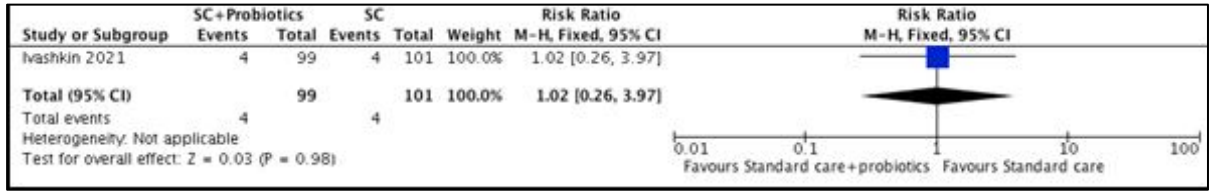


Figure: 5 Forest plot of comparison: SC + Probiotics verses SC, outcome: Deaths

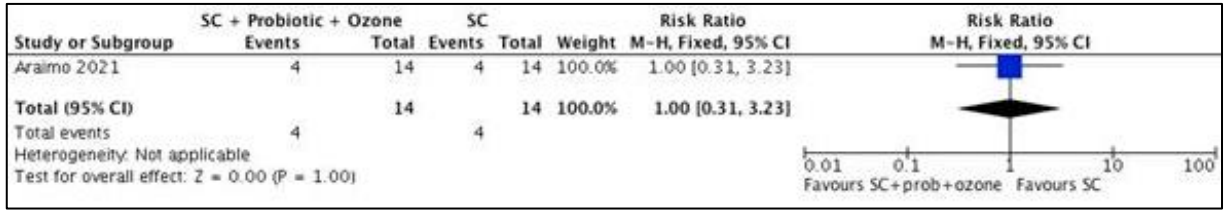
Results

Effects of interventions

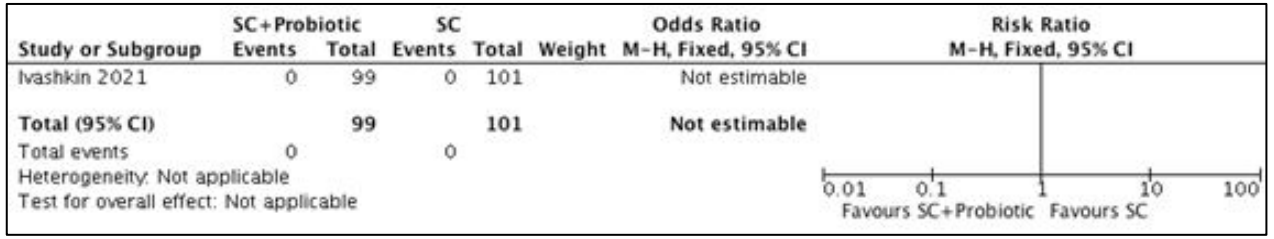
Comparison 1: Probiotics or prebiotics or symbiotics (as an adjunct to standard treatments) verses Standard of care without supplementation of probiotics or prebiotics or symbiotics

5. Adverse events

- One trial reported that the risk of death in different interventions
- Reported that the risk of adverse events was similar in both groups



Forest plot of comparison: SC + Probiotics + Ozone therapy verses SC, outcome: Adverse events



Forest plot of comparison: SC + Probiotics versus SC, outcome: Adverse events

6. Free of fatigue: Rathi et al observed significant reduction in total, Physical and mental fatigue scores in the intervention arm.

Results

Effects of interventions

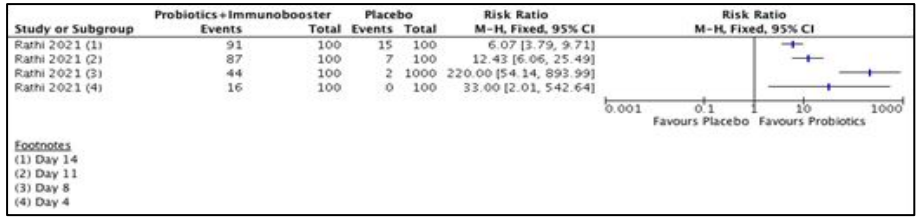
Comparison 2: Probiotics prebiotics or symbiotics (an adjunct to standard treatments) versus Any active comparator (such as appetizers, nutritional supplements, etc.)

We did not find any study that assessed this comparison

Comparison 3: Probiotics or prebiotics or symbiotics (as an adjunct to standard treatments) verses placebo

- **Number of cases of COVID-19, Change in disease severity, Days of hospitalization, Number of deaths, Adverse events:** We did not find any study that assessed this outcome.

- **Free of Fatigue:** Only one study addressed this outcome.
  - Supplemental administration of prebiotics and immune boosters made patients free of fatigue in a significantly greater percentage of subjects in intervention group compared to control arm on day 14
  - Beneficial effect was seen even at earlier time points, with a greater proportion of patients in test arm being fatigue-free on days 4 and 8 than when given on later days.



Forest plot of comparison: Probiotics + Immunoboosters versus Placebo, outcome: Free of fatigue

Results

Quality of evidence

Standard care + Probiotics +Ozone verses Standard care compared to Standard care for Covid-19

Patient or population: Covid-19
Intervention: Standard care + Probiotics +Ozone verses Standard care
Comparison: Standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	GRADE Working Group grades of evidence
	Risk with placebo	The risk with Standard care + Probiotics +Ozone verses Standard care				
Deaths	71 per 1,000	71 per 1,000 (5 to 1,000)	RR 1.00 (0.07 to 14.45)	28 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Adverse events	286 per 1,000	286 per 1,000 (89 to 923)	RR 1.00 (0.31 to 3.23)	28 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: confidence interval; RR: risk ratio.
Explanations:
a. Some concerns in Domain 1 (Randomisation process) and Domain 2 (Deviations from the intended interventions), and a High risk of bias in Domain 5 (Selection of the reported results) of RoB2 Tool.
b. b. There is uncertainty about the results
c. Only one study with relatively few patients

Results

Quality of evidence

Standard care plus probiotics verses standard care compared to Standard care for Covid-19						
Patient or population: Covid-19 **Intervention: Standard care plus probiotics verses standard care** **Comparison: Standard care**						
Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	GRADE Working Group grades of evidence
	Risk with placebo	The risk with Standard care plus probiotics verses standard care				
Deaths	40 per 1,000	40 per 1,000 (10 to 157)	RR 1.02 (0.26 to 3.97)	200 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	High certainty: we are very confident that the actual effect lies close to that of the estimate of the impact. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Adverse events	0 per 1,000	0 per 1,000 (0 to 0)	Outcome not estimable	200 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	
Days of hospitalization	The mean days of hospitalization was 0	MD 0 (2.21 lower to 2.21 higher)	-	200 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	
***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).** **CI: confidence interval; MD: mean difference; RR: risk ratio.** **Explanations:** **a. Some concerns in Domain 1 (Randomisation process) and Domain 2 (Deviations from the intended interventions), and Domain 5 (Selection of the reported results) of RoB2 Tool** **b. There is uncertainty about the result** **c. Only one study with few participants**						

Discussion

Summary of main results

- Evidence in hand suggests that probiotics may make little or no difference in reducing mortality, and days of hospitalization for people with COVID-19, as the observed effect was small and of uncertain clinical significance.
- Therefore, the use of probiotics for the treatment of COVID-19 is currently not evidence-based.
- There was no evidence of increased adverse effects with probiotic use.
- There are currently 31 ongoing trials that can change the findings in the update of this review.
- Several uncertainties persist regarding using probiotics for the prevention and treatment of Covid-19.
- These include : a small number of published studies with relatively few participants, no data on efficacy of probiotics in prevention of Covid-19, and limited data on number of deaths, adverse events, and days of hospitalization.

Discussion

Overall completeness and applicability of evidence

- Number of studies and participants included are limited.
- Findings of this review apply only to currently prescribed probiotic strains such as Lactobacillus and Bifidobacteria species as a single strain or in probiotic mixtures
- Only one study provided data for each of our outcomes of interest.
- This review shows uncertainty arising from suboptimal methodological quality of included trials.
- There is insufficient evidence to confirm whether probiotics can provide a therapeutic advantage in Covid-19 patients.
- Hence, it is hard to draw a definitive conclusion about the effects of probiotics on the prevention and treatment of Covid-19.

Discussion

Potential biases in the review process

- We conducted comprehensive searches to identify all relevant studies. However, some trials may have been missed.
- We did not search the grey literature, thereby missing any conference proceedings/abstracts presented during the rapidly evolving pandemic situation.
- Two of the included trials were open-label, thus affecting the quality of the evidence.
- To avoid bias during the review process, two authors independently undertook screening for the selection of studies, extraction of data, and assessment of the risk of bias in the included studies.
- Disagreements amongst reviewers for risk of bias were resolved through consensus by a third reviewer.
- None of the reviewers was involved in any of the included trials.
- It was not possible to detect the publication bias (2 studies in MA)
- Power to identify overall effect estimate pattern was inadequate, so chance of coincidental findings cannot be omitted.

Conclusions

Implications for practice

- We found low to very low-quality evidence, not conclusive for any implication for practice.
- Evidence in hand suggests that probiotics may make little or no difference in reducing mortality, and days of hospitalization for COVID-19, as the observed effect was small and of uncertain clinical significance.
- The use of probiotics for the treatment of COVID-19 is currently not evidence-based
- There was no evidence of increased adverse effects with probiotic use

Implications for research

- Future studies should better report/measure outcomes such as the number of cases of COVID-19 and the change in disease severity.
- Researchers should also consider standardizing doses/concentrations of probiotics given.
- Methodologically robust RCTs must be undertaken in large samples of populations

Outputs

- Submitted to Frontiers in Nutrition (Q1 Journal)